

HYPERTENSION DURING ANAESTHESIA AND SURGERY

The effects of β -adrenoceptor
blockade and i.v. analgesia

Jóhannes Magnússon



LUND 1985



Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41552414_0042

HYPERTENSION DURING ANAESTHESIA AND SURGERY

**The effects of β -adrenoceptor
blockade and i.v. analgesia**

Jóhannes Magnússon

Leg. läkare

AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Medicinska Fakulteten
vid Lunds Universitet för avläggande av medicine
doktorsexamen kommer att offentligen försvaras i
Föreläsningssal 2, Centralblocket, Lasarettet i Lund,
lördagen den 18 maj, 1985, kl 09.15.

Lund 1985



From the Department of Anaesthesia
(Head: Professor Dag Lundberg)
University Hospital, Lund, Sweden

HYPERTENSION DURING ANAESTHESIA AND SURGERY

**The effects of β -adrenoceptor
blockade and i.v. analgesia**

Jóhannes Magnússon

Lund 1985

© Jóhannes Magnússon 1985

Printed in Sweden

Studentlitteratur

Lund 1985

ISBN 91-7222-869-5

CONTENTS

Summary 5

Introduction 6

Material and Methods 9

patient selection and treatment 9

premedication 11

anaesthesia 11

monitoring devices and measurements 12

biochemical analyses 13

calculations 14

statistics 14

Results 15

effects of i.v. practolol during microlaryngoscopy (ML) (I) 15

effects of 4 days of metoprolol pretreatment before ML (II) 17

effects of narcotic antagonism by naloxone after ML (III) 19

effects of metoprolol pretreatment in hypertensive patients (IV) 21

Discussion 25

microlaryngoscopy 25

studies on hypertensive patients undergoing surgery 29

Conclusions 31

Acknowledgements 32

References 33

Paper I 39

Paper II 45

Paper III 55

Paper IV 61

This thesis is based on the following papers, which will be referred to in the text by Roman numerals:

- I Werner, O., Magnusson, J., Fletcher, R., Nilsson-Ehle, P., and Pahlm, O. I.v. practolol during microlaryngoscopy. Effects on arterial pressure, heart rate, blood glucose and lipolysis.
Br. J. Anaesth., 52: 91, 1980.
- II Magnusson, J., Werner, O., Carlsson, C., Nordén, N., and Pettersson, K-I. Metoprolol, fentanyl and stress responses to microlaryngoscopy. Effects on arterial pressure, heart rate and plasma concentrations of catecholamines, ACTH and cortisol.
Br. J. Anaesth., 55: 405, 1983.
- III Magnusson, J., Werner, O., Carlsson, C., and Pettersson, K-I. Narcotic antagonism by naloxone. Few side-effects after a short procedure?
Anaesthesia, 38: 103, 1983.
- IV Magnusson, J., Thulin, T., Werner, O., Järhult, J., and Thomson, D. Haemodynamic effects of metoprolol pretreatment in hypertensive patients undergoing surgery.
Submitted for publication.

SUMMARY

This thesis describes different attempts to attenuate the cardiovascular responses to stressful stimuli arising during general anaesthesia and surgery. Beta-blockade and i.v. analgesia were used in a series of randomized clinical trials.

In one trial, 13 patients undergoing microlaryngoscopy received the cardioselective beta-blocker practolol i.v., 0.4 mg kg⁻¹, 2 min before thiopentone induction of anaesthesia. A group of 12 control patients received i.v. saline instead. Practolol reduced heart rate but had no significant effect on the hypertensive responses to laryngoscopy.

In another trial, 20 patients undergoing microlaryngoscopy received oral pretreatment for four days with metoprolol 200 mg daily + an additional i.v. dose of 10 mg shortly before anaesthesia. Twenty controls received placebo tablets and i.v. saline instead. Metoprolol reduced heart rate and arterial pressure during intubation and during undisturbed anaesthesia. Variations in arterial pressure during the procedure were of about the same magnitude as among the controls. The opiate analgesic fentanyl, 1.0 mg i.v., markedly attenuated the hypertensive response to microlaryngoscopy. Afterwards the opiate antagonist naloxone, 0.4 mg i.v. + 0.4 mg s.c., was given without provoking side-effects. The lack of side-effects was attributed to microlaryngoscopy being a procedure which does not leave a painful wound, and which is too short for opiate dependence to become established.

The effects of beta-blockers were studied in 30 hypertensive patients undergoing gallbladder surgery or hernia repair. Half of them received metoprolol, 200 mg daily for 2-5 weeks before surgery and 15 mg i.v. shortly before anaesthesia. The others received placebo tablets and saline. Metoprolol reduced heart rate and arterial pressure during intubation and undisturbed anaesthesia. After surgery commenced, arterial pressure and systemic vascular resistance increased markedly in both groups, while cardiac index decreased in the metoprolol group. After extubation, heart rate, arterial pressure and cardiac index were all significantly less among patients given metoprolol. The drug was well tolerated except that marked bradycardia (26 min⁻¹) was observed after neostigmine in one patient.

INTRODUCTION

During general anaesthesia, tachycardia, arrhythmia and hypertension are commonly observed cardiovascular responses to noxious stimuli. This kind of stimulation occurs during e.g. laryngoscopy and intubation and during various surgical manoeuvres such as skin incision, sternotomy and traction on viscera. Concomitantly with the cardiovascular response, a neurohumoral stress response may occur with increases in e.g. plasma catecholamine, ACTH and cortisol concentrations.

The arterial pressure response to surgical stimuli is particularly pronounced in patients with preoperative hypertension, and has been associated with serious complications in susceptible patients (Fox et al, 1977). Attempts to attenuate the cardiovascular responses have included blockade of the afferent fibres, e.g. epidural or spinal anaesthesia (Roizen et al, 1981a), increase in anaesthetic depth by volatile anaesthetics or i.v. analgetics (Roizen et al, 1981b; Stanley et al, 1979; Martin et al, 1982), and topical oropharyngeal or i.v. administration of lidocaine (Stoelting, 1977; Hamill et al, 1981).

Beta-adrenoceptor blockers have also been suggested as useful agents for attenuating the cardiovascular stress responses. I.v. betablockers decrease the incidence of arrhythmia and tachycardia caused by stressful stimuli during anaesthesia and surgery (Rollason and Russel, 1980), but conflicting results have been obtained as regards protection against increases in arterial pressure (Prys-Roberts et al, 1973; Ryhänen et al, 1977; Siedlecki, 1975). A strictly randomized clinical trial on the effects of acute pretreatment with i.v. betablockade shortly before anaesthesia was lacking, and study I was designed to fill the gap. It was

found that the cardioselective betablocker practolol reduced heart rate, but had a rather small effect on the arterial pressure response to stressful stimuli. It was asked whether a longer term of pretreatment might give different results and in study II, four days of pretreatment with metoprolol, which is also a cardioselective betablocker, was tried.

Studies I and II were done on patients undergoing microlaryngoscopy (ML). This procedure may cause an intense circulatory stress response that is usually rather short, and does not leave a painful wound. Opiates decrease the arterial pressure response to intubation (Dahlgren and Messeter, 1980; Martin et al, 1982) and to surgical stimuli (Stanley et al, 1979), if adequate i.v. doses are given. In spite of this, opiates are often used sparingly to avoid the necessity for giving opiate antagonists, e.g. naloxone, after the anaesthetic. This is because serious side-effects to naloxone, such as hypertension (Estilo and Cottrell, 1981), dysrhythmia (Azar and Turndorf, 1979; Michaelis et al, 1974), pulmonary oedema (Flacke et al, 1977) and vomiting (Longnecker et al, 1973) have been reported. These complications occurred after surgery lasting at least a couple of hours and which left a painful wound, and it was reasoned that the risk of side-effects to naloxone might be less after ML. These aspects were studied in paper III.

Papers I-III were about stress responses, particularly hypertensive responses, during anaesthesia and surgery in patients most of whom were previously normotensive. In paper IV the use of betablockade in hypertensive patients undergoing surgery was studied. Although it is generally agreed that antihypertensive treatment should not be abruptly withdrawn before anaesthesia and surgery (Pontén et al, 1982) it is still controversial whether it is beneficial to initiate preoperative treatment in

previously untreated hypertensive patients. Goldman and Caldera (1979) found no evidence that patients with mild to moderate hypertension benefited from preoperative antihypertensive treatment, while Prys-Roberts and others (1973), who mainly studied patients with more severe hypertension, found improved cardiovascular stability during anaesthesia by using betablockers. There were no previous randomized trials in hypertensive patients undergoing surgery, and study IV was carried out as a double-blind comparison between metoprolol pretreatment (2-5 weeks) and placebo.

MATERIAL AND METHODS

Sixty-five chiefly normotensive patients, aged 22-79 years, undergoing microlaryngoscopy (ML) (I, II, III) and 30 hypertensive patients, aged 34-70 years, scheduled for cholecystectomy or hernia repair (IV) were investigated.

Patient selection and treatment

Paper I. Twenty-five patients, aged 22-73 years, undergoing diagnostic or therapeutic microlaryngoscopy (ML) by the Kleinsasser technique, were studied. A physical examination, an ECG and a chest X-ray were made on the day before the procedure. Patients with diabetes, obstructive lung disease, upper airway obstruction, previous myocardial infarction, congestive heart failure, second or third degree A-V block were excluded, as were patients receiving digitalis, diuretics, antihypertensive or anti-arrhythmic drugs. The patients were subsequently randomly divided into two groups. The treatment group ($n = 13$) received practolol 0.4 mg kg^{-1} i.v. 2 min before induction and 0.2 mg kg^{-1} during anaesthesia if this lasted more than 12 min. The control group ($n = 12$) was given equivalent volume of saline instead.

Papers II and III. Forty patients, aged 39-79 years, undergoing ML were studied. The exclusion criteria were the same as in paper I. A physical examination was done 3 days before the procedure, at which time the patients were divided in four groups of ten by stratified randomization according to age (55 years or less, or greater than 55 years) and the value of their systolic arterial pressure (150 mm Hg or less, or greater than 150 mm Hg). The groups in paper II were:

1. Controls. These patients received thiopentone and nitrous oxide as the only anaesthetics.
2. Patients in this group received thiopentone and nitrous oxide as in group 1. In addition, they were given fentanyl 1.0 mg i.v. shortly before ML and 0.5 mg after 20 min of ML if it lasted that long. Naloxone 0.4 mg i.v. + 0.4 mg s.c. was administered after surgery.
3. Patients in this group received metoprolol 200 mg, in a slow released form, once daily for 4 days. The first tablet was given in the afternoon shortly after the patient had been examined and the last tablet at 6 a.m. on the day of operation. An additional 10 mg was given i.v. 1-3 min before anaesthesia. The technique of anaesthesia was as in group 1.
4. Patients in this group received metoprolol (as group 3). However, the the technique of anaesthesia was the same as in group 2.

Paper III draws its data from half of the material of paper II. Groups 1 and 2 were compared.

Paper IV. 294 patients, aged 30-70 years, scheduled for cholecystectomy or hernia repair were screened. Those with systolic arterial pressure (SAP) above 170 mm Hg or diastolic arterial pressure (DAP) above 100 mm Hg, and those already receiving antihypertensive treatment, were referred to a physician at the department of internal medicine for further examination. The presence of hypertension was confirmed by repeated arterial pressure measurements. A medical history was obtained and a physical examination, a chest X-ray and an ECG, were done. Patients with obstructive lung disease, previous myocardial infarction, congestive heart failure or second and third degree A-V block were excluded. Thirty suitable patients (age 34-70 years), were found. Of these, 13 were previously untreated. In the remaining 17, antihypertensive therapy (betablocking drugs and/or

diuretics, vasodilators and alpha-adrenoceptor agonist) was gradually withdrawn during a week of close medical supervision. After a withdrawal period of 2-3 weeks, the patients were subsequently divided into two groups of fifteen by stratified randomization according to age (above or below 60 years) and mean arterial pressure (MAP) (above or below 125 mm Hg). The treatment group received metoprolol tablets 200 mg in a slow release form, once daily for at least two weeks (mean 21 days, range 14-34) up to and including the morning of operation. In addition metoprolol 15 mg was given i.v. shortly before anaesthetic induction. The controls received placebo tablets and equivalent volume of saline instead. Two patients in the treatment group and one patient in the control group were subsequently excluded because of complications during the treatment period.

Premedication

The patients were premedicated with morphine (2.5-15 mg) and hyoscine (0.1-0.6 mg) i.m. according to age, about one hour before arrival in the operating room (I-IV).

Anaesthesia

Anaesthesia was induced with thiopentone ($4-5 \text{ mg kg}^{-1}$) (I, II, III) or fentanyl ($4 \text{ } \mu\text{g kg}^{-1}$), followed by thiopentone ($2-3 \text{ mg kg}^{-1}$) (IV). Endotracheal intubation [Portex cuffed 6.5 (I, II, III) or 8 to 9 mm internal diameter (IV) lubricated with xylocaine gel] was performed with suxamethonium (1 mg kg^{-1}) (I, II, III) or pancuronium

(0.1 mg kg⁻¹) (IV) as muscle relaxants. The laryngoscope (MacIntosh) was held in place to visualize the vocal cords for exactly 30 s (II, III, IV). Subsequently, the lungs were ventilated manually (I, II, III) or mechanically (Servo ventilator, Siemens Elema) (IV) with 70 % nitrous oxide in oxygen.

In paper I, fentanyl 0.1-0.2 mg was given if SAP was 200 mm Hg or greater. In papers II and III, fentanyl was given to groups 2 and 4 (see "patient selection and treatment"). After the end of ML, naloxone hydrochloride was given to these patients. The others received saline instead. In papers I, II and III muscle relaxation during ML was obtained with an infusion of suxamethonium. In paper IV, anaesthesia was maintained with N₂O/O₂ supplemented with fentanyl 2 µg kg⁻¹ shortly before surgery. Another 1.5 µg kg⁻¹ was administered after 25-30 min of surgery, and thereafter intermittently every 30-45 min. Muscle relaxation was obtained with pancuronium. Patients undergoing cholecystectomy received intercostal blockade with 0.5 % bupivacaine at the end of the operation. Subsequently, muscle relaxation was reversed by giving atropine (1.0-1.5 mg) and neostigmine (2.0-3.0 mg) i.v. (IV).

Monitoring devices and measurements

On the morning of surgery (I) or 3 days (II, III) and 2-5 weeks (IV) before anaesthesia, measurements of arterial pressure by upper arm sphygmomanometry and heart rate (HR) was made after 10 min of supine rest.

In paper I, ECG (modified lead V₅) was obtained continuously on a portable recorder (SRA, Sweden) and systolic arterial pressure was measured by radial artery palpation and recorded every minute during anaesthesia. The observer did not know the nature of the treatment. In papers II, III and IV, ECG and systemic arterial pressure were recorded continuously on an ink-jet recorder (Mingograph 81) along with pulmonary arterial pressure (IV). Systemic and pulmonary arterial pressures were measured by calibrated transducers (HP 1280 C, Hewlett Packard), via an indwelling catheter in the radial (II, III) or brachial artery (IV) and via a triple lumen balloon-tipped pulmonary arterial catheter (IV). Central venous pressure (CVP) was measured via the side hole and pulmonary arterial occlusion pressure (PAOP) by inflating the balloon. Cardiac output was obtained in duplicate or triplicate with a thermodilution computer (IL 701, Instrumentation Laboratory). The thermodilution curves were recordered (IL 702, Instrumentation Laboratory), so that artifacts could be detected (IV). A CO₂ analyzer (CO₂ Analyzer 930, Siemens-Elma, Sweden) was used to measure expired CO₂ concentration (IV).

Biochemical analyses

Blood samples were withdrawn from a peripheral venous cannula (I) or an arterial cannula (II, IV) into prechilled test tubes and immediately immersed in ice-cold water. Plasma was separated few minutes later by centrifugation and stored at -70° (II, IV) or -20° C (I) until assay. Blood glucose (I) was analysed within 6 h by enzymatic-colorimetric method (Marks, 1959). Glycerol concentrations (I) were measured by an enzymatic-fluorometric method (Laurell and Tibbling, 1966). Adrenaline and noradrenaline concentrations (II) were measured by a radioenzymatic assay

(Peuler and Johnsson, 1977), slightly modified according to Eriksson (1981). ACTH was determined by radioimmunoassay (CIS-Sorin, France) and cortisol by solid phase radioimmunoassay (Clinical Assay, Mass., USA) (II). Metoprolol concentrations in plasma (II, IV) were measured as described by Ervik (1975). Blood samples for blood gases (IV), were taken in heparinized plastic syringes and analysed within 10 min (IL 413 Blood gas Laboratory, Instrumentation Laboratory).

Calculations

MAP before treatment was calculated as $SAP \times 1/3 + DAP \times 2/3$. On other occasions, MAP was estimated from the arterial pressure tracing (II, III). In paper IV, both the unfiltered pressure tracing and a damped curve representing mean pressure were recorded (Werner and Benthin, 1982) so that MAP and mean pulmonary arterial pressure (MPAP) could be obtained directly. All analyses of the curves were done by an observer, who did not know the nature of the treatment. Cardiac index (CI) was obtained by dividing cardiac output with body surface area (DuBois and DuBois, 1916). Systemic vascular resistance index (SVRI) was obtained as: $(MAP - CVP)/CI$ and pulmonary vascular resistance index (PVRI) as: $(MPAP - PAOP)/CI$ (IV). Rate-pressure product was calculated as $SAP \times HR$.

Statistics

The Wilcoxon (two-sided) rank sum test for paired data was used for within-group comparisons. The Mann-Whitney (two-sided) rank sum test for unpaired data was used for between-group comparisons. In paper I, II and

III changes in heart rate and arterial pressure in relation to resting values in the untreated patient were compared, rather than the directly recorded values. This was in order to decrease the effects of inter-individual variation. In paper IV the statistical analysis was done on the directly recorded values. This was because the haemodynamic studies were more extensive, and included cardiac index and pulmonary arterial pressures. However, these measures could not be obtained before the start of placebo or metoprolol treatment.

RESULTS

The patients in the control and treatment groups were very similar except in paper IV, where the controls weighed more than those in the treatment group. Thus, the six patients who weighed 100 kg or more were all allotted to the control group. In order to assess whether this skewness affected the conclusions, the data were analysed with these patients both excluded and included. In both cases, the haemodynamical findings were essentially the same.

Effects of i.v. practolol during microlaryngoscopy (ML) (I) (fig 1)

Systolic arterial pressure (SAP) was similar in the treated and untreated patients before induction of anaesthesia. Practolol had no significant effect on the awake patient, but SAP decreased more during induction among treated than among untreated patients ($p < 0.05$). Maximum SAP within 2 min after laryngoscopy and intubation was high and there was no statistically significant difference between the groups. Also during ML, SAP was

markedly increased in both groups. Practolol attenuated the HR response to intubation, ML and extubation ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively).

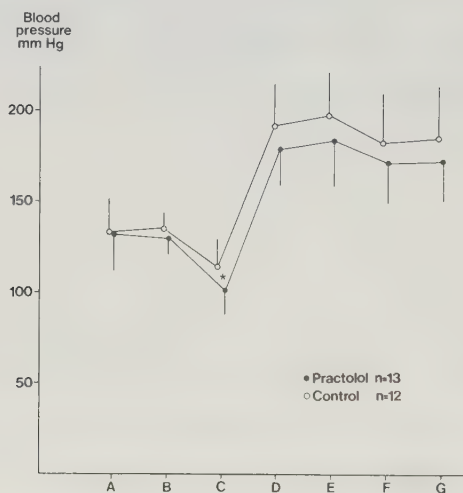


Fig 1. Effects of i.v. practolol. Systolic arterial pressure before and during microlaryngoscopy is shown (groups mean and 1SD). A = Immediately before injections; B = 1 min after injection of atropine and practolol (saline). Patient still awake; C = lowest value recorded during induction (this always occurred before intubation); D = greatest value within 2 min after laryngoscopy and intubation; E = greatest value during microlaryngoscopy; F = mean value during microlaryngoscopy; G = 2 min after repeated injection of practolol 0.2 mg kg⁻¹ or saline. Significant differences between groups are indicated, * = $p < 0.05$.

During ML, blood-glucose concentration increased by 0.2 ± 0.7 mmol l⁻¹ in the control group (n.s.) and by 0.4 ± 0.7 mmol l⁻¹ in the treatment group ($p < 0.05$). There was no significant difference between the groups. There was no significant difference in plasma glycerol concentrations between the groups, nor were there any significant changes within the groups.

Effects of 4 days of metoprolol pretreatment before ML (II) (fig 2)

Mean MAP was similar among the treated and untreated patients before metoprolol or placebo. Before anaesthesia, MAP was 14 mm Hg less among those given metoprolol than among the others (n.s.). Compared to placebo, metoprolol reduced MAP both early during induction ($p < 0.05$), during laryngoscopy and intubation ($p < 0.01$) and during undisturbed anaesthesia immediately before ML ($p < 0.01$). The reduction in MAP during ML and after extubation was not significant. Fentanyl markedly decreased MAP during undisturbed anaesthesia and its effect on MAP during ML was also pronounced.

Metoprolol significantly decreased HR before ($p < 0.01$), during ($p < 0.01$) and after ($p < 0.01$) anaesthesia. Fentanyl had no significant effect on heart rate.

Mean values of plasma adrenaline and noradrenaline concentrations before anaesthesia were slightly above the normal range for resting relaxed subject (Eklund et al, 1983). Adrenaline decreased during anaesthesia, significantly so in most groups, and increased again during ML. The increase was less pronounced among patients given fentanyl (group 2 and 4) than in the others. There were no significant differences between the

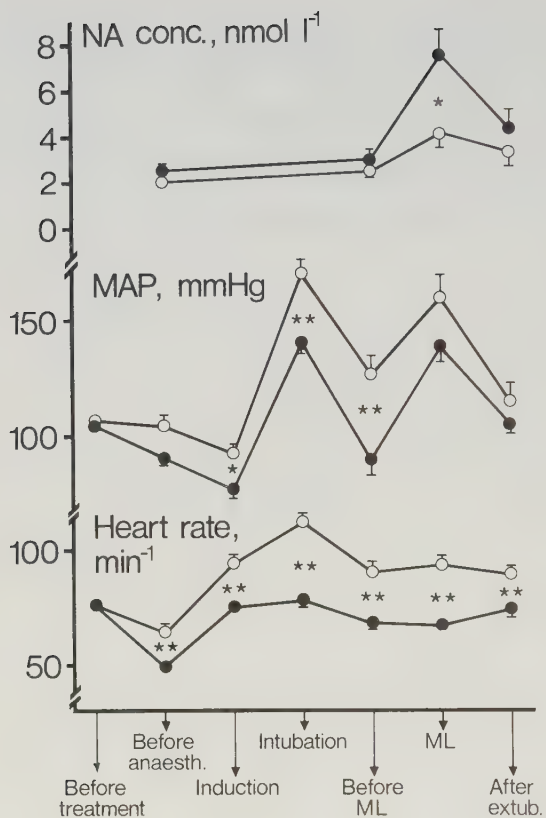


Fig 2. Effects of four days of metoprolol pretreatment. Plasma noradrenaline (NA) concentrations, mean arterial pressure (MAP) and heart rates among patients receiving metoprolol (●) or placebo (○) are compared. Group mean and 1 SEM. Measurements were taken on the following occasions: at rest during the preoperative visit before starting metoprolol or placebo; about 5 min before anaesthesia; at minimum MAP during induction, but before intubation; at maximum MAP within 3 min after intubation; after 10 min of microlaryngoscopy (ML), or 2 min before the end of ML, whichever came first; about 5 min after extubation. Significant differences between patients given metoprolol, and those given placebo: * $p < 0.05$; and ** $p < 0.01$.

metoprolol treated patients and the others. Mean values of plasma noradrenaline concentration increased in all groups during ML, with significantly greater values in patients given metoprolol but not fentanyl (group 3) than among controls ($p < 0.05$). There was a significant difference ($p < 0.01$) also between group 3 and group 4 (both metoprolol and fentanyl).

Mean values of plasma ACTH and cortisol concentrations increased significantly during ML among patients given saline instead of fentanyl. At this stage, the plasma concentration of cortisol was less ($p < 0.05$) among the metoprolol treated patients than among the untreated patients - a reverse relationship compared with the plasma noradrenaline concentration. No significant difference in ACTH was found between the metoprolol treated and the untreated patients during ML.

Effects of narcotic antagonism by naloxone after ML (III) (fig 3)

MAP was similar in the two groups before anaesthesia. Mean MAP during microlaryngoscopy was 159 mm Hg among the controls and 105 mm Hg among patients given fentanyl ($p < 0.01$). A significant difference in MAP, of 35 mm Hg, remained after microlaryngoscopy, immediately before naloxone or saline ($p < 0.01$). Mean MAP increased by 20 mm Hg during the first 2 minutes after naloxone ($p < 0.01$), there being a further increase by 8 mm Hg (not significant) up to the point 5 minutes after extubation. During the same period, MAP tended to decrease among the controls. However, there were no significant differences between the groups at any time after naloxone (or corresponding volumes of saline). Neither heart rate nor the incidence of supraventricular extrasystoles or ventricular extrasystoles were significantly different in the two groups.

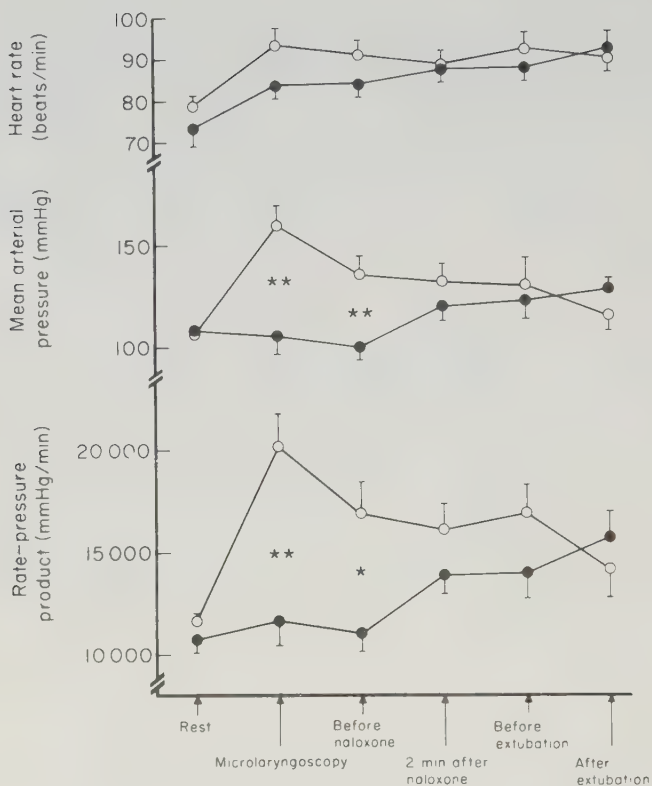


Fig 3. Effects of fentanyl and naloxone. Cardiovascular changes during and after microlaryngoscopy are shown. Group mean and 1 SEM: Measurements were taken on the following occasions: at rest during the preoperative visit; after 10 min of microlaryngoscopy or 2 min before the end of microlaryngoscopy, whichever came first; immediately before naloxone, i.e. about 3 min after microlaryngoscopy; 2 min after naloxone, immediately before extubation, i.e. about 5 min after naloxone; 5 min after extubation. Significant differences between groups on each occasion are indicated, * = $p < 0.05$, ** = $p < 0.01$. (○) = control; (●) = fentanyl + naloxone.

No patient vomited or complained of nausea during the observation period in the operating room (15 min after extubation). However, one patient of each group complained of nausea in the hours some hours after anaesthesia. No patients needed extra naloxone.

Effects of metoprolol pretreatment in hypertensive patients (IV) (fig 4)

Before starting metoprolol or placebo, both groups had similar MAP and HR. There was no difference in MAP between patients who had previous antihypertensive treatment, which had been withdrawn 2-3 weeks earlier, and those who were not previously treated (129 ± 12 and 128 ± 8 , respectively).

Before anaesthesia, MAP had decreased significantly ($p < 0.01$) in the metoprolol group, although the difference between the groups was not significant. At this stage both groups had similar values of CI, SVRI, PAOP, CVP and MPAP. During intubation, metoprolol attenuated the increase in MAP (6 mm Hg) compared to the untreated patients (29 mm Hg). MAP was also significantly less in the metoprolol group during undisturbed anaesthesia ($p < 0.05$) and after extubation ($p < 0.01$). The difference in arterial pressure after 20 minutes of surgery was not quite significant. MAP increased similarly in both groups in response to surgery.

Hypertensive episodes (SAP > 200 mm Hg, or an increase in SAP > 50 mm Hg) in response to surgery, were seen in 5 out of 13 metoprolol treated patients and in 10 out of 14 patients of the control group. Two of the latter were treated with sodium nitroprusside infusion in addition to fentanyl supplementation, to keep the arterial pressure down. Hypotensive

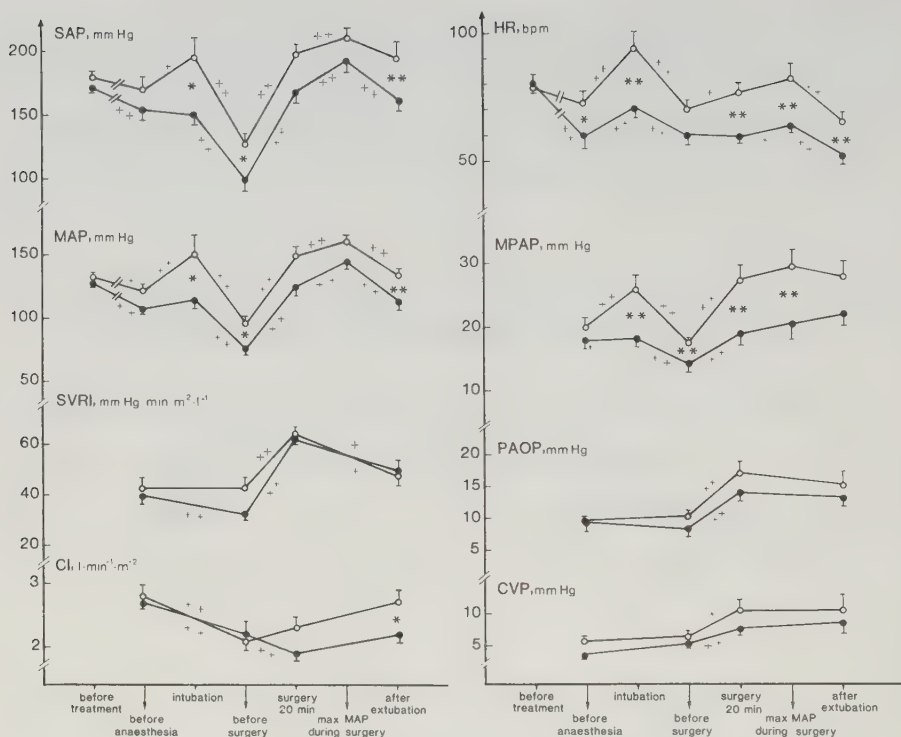


Fig 4. Effects of 2-5 weeks of metoprolol pretreatment. Haemodynamic values among hypertensive patients receiving metoprolol (●) or placebo (o) are compared. Group mean and 1 SEM. Measurements were taken on the following occasions: at the preoperative visit shortly before starting metoprolol or placebo treatment; about 10 min before anaesthesia; at maximum mean arterial pressure (MAP) observed shortly after intubation; during undisturbed anaesthesia; after 20 min of surgery; at maximum MAP during surgery; about 5 min after extubation. Significant differences between groups are indicated: * = $p < 0.05$, ** = $p < 0.01$. Significant changes between successive stages, within each group, are indicated as + = $p < 0.05$, ++ = $p < 0.01$.

episodes (SAP < 70 mm Hg) were seen in one patient of the control group and in two patients of the metoprolol group. In the recovery room mean SAP was 15-25 mm Hg less in the metoprolol treated patients.

HR was significantly reduced by metoprolol. After injection of neostigmine and atropine, a HR below 40 min⁻¹ was observed in 4 patients receiving metoprolol (minimum 26 min⁻¹) but not among the controls. Additional atropine was given, but in the patient with the lowest heart rate, this remained low.

Cardiac index (CI) decreased ($p < 0.01$) similarly in both groups during undisturbed anaesthesia. In response to surgery a further decrease of 0.3 l min⁻¹ m⁻² ($p < 0.01$) was seen among patients given metoprolol. There was no significant increase in mean CI among the controls nor was the difference between the groups significant. After extubation CI was significantly less in the metoprolol group ($p < 0.05$).

Systemic vascular resistance index (SVRI) decreased during undisturbed anaesthesia among those receiving metoprolol ($p < 0.01$). The difference between the groups was not significant. In response to surgery, marked increases in SVRI were seen in both groups ($p < 0.01$) with no significant difference between the groups.

Central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP) increased in response to surgery in both groups. Among the metoprolol treated patients there was a significant correlation between the increase in PAOP and the increase in MAP in response to surgery ($r = 0.72$, $p < 0.01$). A similar correlation was found between the increase in PAOP and increase in SVRI ($r = 0.69$, $p < 0.01$). No such correlation was found

among the untreated patients, although they showed a similar increase in mean PAOP during surgery.

Mean pulmonary arterial pressure (MPAP) was similar in both groups before anaesthesia, but was significantly less ($p < 0.01$) in metoprolol treated patients during all stages of anaesthesia and surgery. Pulmonary vascular resistance index (PVRI) was slightly less in the metoprolol group with a significant difference during surgery ($p < 0.05$).

Before anaesthesia, PaCO_2 was significantly greater in the metoprolol treated patients than in untreated patients ($p < 0.05$). In spite of a similar ventilatory minute volume in relation to body surface area in both groups during anaesthesia, mean PaCO_2 was 0.3-0.5 kPa greater among the controls. After extubation, there was slight hypoventilation in patients receiving metoprolol, whose mean PaCO_2 was 0.7 kPa greater than that of the controls ($p < 0.05$). PaO_2 values were similar in both groups before, during and after anaesthesia.

DISCUSSION

The main object of the studies was to investigate whether betablockade is suitable for use in attenuating circulatory responses to stressful stimuli arising during anaesthesia and surgery (I,II,IV). As a "spin-off" from the studies, a somewhat novel anaesthetic technique for microlaryngoscopy and bronchoscopy was devised (III). Microlaryngoscopy was studied (I-III) because there is often a marked cardiovascular stress response in lightly anaesthetized subjects (Hjort Sørensen et al, 1981), similar to that seen during laryngoscopy and intubation (Weigand, 1970). Hypertensive patients were studied during cholecystectomy and hernia repair (IV) because these are relatively short and common surgical procedures in a middle-aged population.

Microlaryngoscopy

Although the effect of betablockers on the heart rate is directly related to the plasma concentration of the drug (van Bahr et al, 1976) the relation between plasma concentration and arterial pressure is less direct (Bengtsson et al, 1975). Thus, 10 mg propranolol i.v. reduces heart rate but not arterial pressure (Tarazi and Dustan, 1972). The full antihypertensive effect of betablockers is seen first after a few hours or days of treatment (Conway and Amery, 1975; Haglund and Collste, 1980). Our findings in respect of the effects of acute treatment with i.v. practolol (I) and four days of metoprolol pretreatment (II) are consistent with these studies. Thus, practolol did not appreciably reduce arterial pressure, while metoprolol did. However, both practolol and metoprolol decreased the heart rate. Neither kind of treatment affected greatly the

fluctuations in mean values of arterial pressure during anaesthesia. This agrees with findings in awake patients under acute stress (Nicotereo et al, 1968; Nyberg et al, 1977). Siedlecki (1975), who gave the same dose of practolol (0.4 mg kg^{-1}) i.v. before thiopentone induction was also unable to demonstrate any effect on the arterial pressure response to laryngoscopy and intubation. Similarly, Pontén and others (1982) found that variations in arterial pressure during anaesthesia and surgery were not reduced by continuing, instead of withdrawing, betablocking therapy. By contrast, Prys-Roberts and others (1973), who studied hypertensive patients under halothane-nitrous oxide anaesthesia, found that decreases and increases in arterial pressure were attenuated both by acute pretreatment with i.v. practolol, and by two days of oral pretreatment. The discrepancy between their results and ours may be explained by the type of anaesthesia and by the fact that other antihypertensive drugs besides practolol were used. Halothane is known to decrease the myocardial contractility (Prys-Roberts et al, 1972) and the betablocker may have potentiated the effect of halothane.

The use of fentanyl for ML, followed by naloxone afterwards was also investigated (III). 1.0 mg fentanyl offered effective protection against hypertension during ML. After naloxone (saline), arterial pressure and heart rate were similar in the fentanyl + naloxone group and the control group. In other studies nausea and vomiting have been frequent after administration of naloxone, when used to antagonise the effects of opiates (Longnecker et al, 1973; Meyer and Sparber, 1977; Nutt and Jasinski, 1974; Evans et al, 1974). These side-effects and the adverse circulatory response (Estilo and Cottrell, 1981; Azar and Turndorf, 1979; Michealis et al, 1974; Flacke et al, 1977) reported after narcotic supplemented anaesthesia followed by naloxone can partly be explained as withdrawal

phenomena (Martin, 1976). The results in the present study (III) are in contrast to these findings. No patient vomited after naloxone and there was little evidence for a circulatory "overshoot reaction". The discrepancy between our findings and those reported above can be explained by one or all of the following points. Firstly, hyoscine, which was used for premedication, has anti-emetic properties (Wood-Smith et al, 1973). Second, the major dose of fentanyl was administered less than 30 min before naloxone. It is unlikely that such a short exposure induces dependence to narcotic analgesics. Third, postoperative pain was probably minimal among the patients.

In our hospital, the technique for ventilating the lungs during ML is at present somewhat different from that used in studies I-III. The inspired gas is nowadays supplied by a high frequency ventilator (Bronchovent, AGA) through a thin nasotracheal catheter (Eriksson and Sjöstrand, 1977). The working conditions for the surgeon are better than with ventilation through a conventional cuffed endotracheal tube, but there is the drawback that inhalational anaesthetics are not used in order to avoid pollution of the operating room. This has emphasized the need for an intravenous technique which ensures adequate anaesthesia during ML. The anaesthetic technique currently used by the author is very similar to that described in paper III, i.e. moderate doses of thiopentone and adequate doses of fentanyl (0.4-0.8 mg) are given. Afterwards, a large dose of naloxone is injected i.v. + s.c. My experience from hundreds of anaesthetics is, that this may be done without provoking nausea, vomiting or serious circulatory side effects. Late respiratory depression (Adams and Pybus, 1978) serious enough to require additional naloxone has not been seen, but to reduce this potential risk the author plans to exchange fentanyl for the more short-acting new synthetic opiate alfentanil when this becomes available. Alfentanil has not yet been approved for use in Sweden.

Effects on metabolism and stress hormones. Non-selective betablockers have been shown to attenuate the hyperglycaemic and lipolytic response to stress (Taggart and Carruthers, 1972). In study I, a slight hyperglycaemic response to ML was observed, which was not affected by i.v. practolol. The betablocker had no significant effect on plasma glycerol concentration. This agrees with other observations, which have shown that cardioselective betablockers (practolol, metoprolol) have little or no inhibitory effect on lipolysis (Gibbson et al, 1976; William-Olsson et al, 1979).

During ML, plasma catecholamine concentrations were high in patients not receiving fentanyl, which indicates high sympathetic activity. Rather remarkably, mean plasma noradrenaline concentrations among patients given metoprolol but not fentanyl (group 3, (II)) were almost twice those of the controls (group 1) (fig 2). Similar results have been found in metoprolol treated patients during dynamic exercise (Hansson et al, 1977). One possible explanation for these results is that removal of noradrenaline from plasma is slowed by betablockers (Esler et al, 1981). Therefore, the difference in noradrenaline concentrations between the metoprolol treated patients and the controls (groups 1 vs 3, (II)) does not necessarily reflect a difference in overall sympathetic activity. Plasma noradrenaline concentrations were not increased among those metoprolol treated patients who also received fentanyl, probably because of central inhibition of sympathetic activity by fentanyl.

The attenuated ACTH and cortisol response among patients given fentanyl during ML and the increase in ACTH after naloxone may be explained by a direct inhibition of ACTH release by opiates (Volavka et al, 1979; Grossman and Besser, 1982).

Studies on hypertensive patients undergoing surgery

It is not uncommon that hypertension is discovered only shortly before the intended time for surgery. This poses a problem for the anaesthetist, who will have to decide whether to manage without treatment, whether to institute a short term of treatment with a drug and dosage believed suitable, or whether to postpone surgery so that antihypertensive treatment can be optimized, a procedure which may take several months. Although these matters have been widely discussed, there have been no randomized trials to determine the advantages and disadvantages of various policies. With the present study, we aimed at comparing the first and second of these alternatives. We chose a cardioselective betablocker, since this is the commonest type of antihypertensive drug in Sweden and several other countries. In addition, Prys-Roberts and others (1973) found that pretreatment with a cardioselective betablocker (practolol) improved haemodynamic stability in anaesthetized hypertensive patients.

Metoprolol pretreatment significantly reduced arterial pressure during endotracheal intubation, which agrees with the findings in paper II. It has been suggested (Prys-Roberts et al, 1973), that betablocker pretreatment reduces the arterial pressure response to intubation. This has since been corroborated by others as regards long term pretreatment (Pontén et al, 1982) although the suggestion that acute i.v. betablocker pretreatment reduces arterial pressure during intubation has not been confirmed (paper I; Siedlecki, 1975). Thus, it appears that a single i.v. dose of betablocker may be less effective than a longer term of pretreatment in attenuating the hypertensive response to intubation.

In the present study, 2-5 weeks of metoprolol pretreatment significantly reduced arterial pressure also during undisturbed anaesthesia and after extubation. There was a similar, but not quite significant difference during surgery. The drug did not attenuate the increase in arterial pressure in response to surgery, nor did it significantly attenuate the variations in SVRI. These findings are similar to those of Pontén and others (1982). However, the findings do not agree with those by Prys-Roberts and co-workers (1971), who studied treated and untreated hypertensive patients in a non-randomized study. Exact comparison with the latter study is difficult, however, because haemodynamics during surgery were not assessed and because antihypertensive treatment was with drugs other than betablockers, such as bethanidine, methyldopa and reserpine.

As surgery commenced, CI decreased significantly in the metoprolol group, while it was unchanged among the controls. Furthermore, the increase in PAOP in the metoprolol group was significantly correlated to the increase in SVRI and MAP. This might indicate that the betablocked heart could not respond adequately to the increased afterload, but on the other hand the mean increase in PAOP at this stage was as great among the controls. Furthermore, no patient had signs of heart failure during surgery and the patient who had heart failure after extubation (IV) belonged to the controls.

PaCO₂ was significantly higher in the metoprolol treated patients before anaesthesia and after extubation. This may be due to an effect on the central nervous system. In fact, some authors have found that betablockers may depress the ventilatory response to CO₂ provocation (Mustchin et al, 1976; Patrick and Pearson, 1980) although others disagree (Folgering and Braakhekke, 1980; Leitch et al, 1980).

CONCLUSIONS

I.v. pretreatment with the cardioselective betablocker practolol immediately before anaesthesia attenuated the heart rate response to intubation and microlaryngoscopy but had little effect on the hypertensive response.

Four days of pretreatment with the cardioselective betablocker metoprolol before microlaryngoscopy decreased heart rate and arterial pressure during anaesthesia, but did not markedly affect the fluctuations in arterial pressure during the procedure. Metoprolol enhanced the increase in plasma noradrenaline concentration caused by microlaryngoscopy.

Fentanyl blunted the hypertensive response and decreased plasma ACTH and cortisol concentration during microlaryngoscopy.

After microlaryngoscopy, the effects of fentanyl could be antagonized by large doses of naloxone without causing serious side-effects.

In hypertensive patients, 2-5 weeks of metoprolol pretreatment decreased arterial and pulmonary arterial pressure during intubation, during undisturbed general anaesthesia and after extubation. Metoprolol had little effect on fluctuations in systemic vascular resistance, arterial pressure, pulmonary arterial occlusion pressure or central venous pressure in response to surgical stimuli. Metoprolol was well tolerated except for a few cases of bradycardia after neostigmine.

ACKNOWLEDGEMENTS

This thesis emanates from the Department of Anaesthesia, University Hospital, Lund, Sweden.

I would like to thank the staff and my colleagues of the Departments of Anaesthesia, ENT-surgery, Internal Medicine and Surgery for good cooperation and valuable support during the study. Special thanks to: Thomas Thulin and Christer Carlsson for stimulating cooperation; Lars Nordström and Roger Fletcher for constructive criticism; Professor Gillis Johnsson and colleagues at Hässle/Astra for support and helpful suggestions; Ingrid Svenstam, Anders Beckman and Gunvor Ekdahl for excellent technical assistance; Monica Vikingsson and the secretaries at the Department of Anaesthesia for typing the manuscripts.

I am indebted to Professor Emeritus Eric Nilsson and Professor Dag Lundberg for providing me with the opportunity to do this work.

I wish to express my warmest thanks to Assistant Professor Olof Werner, my tutor, for his invaluable support and encouragement which were of great value for the completion of this thesis.

Finally, my warmest thanks to my family for giving me time for this work.

These studies were financially supported by grants from the Medical Faculty, University of Lund and the Åke Wiberg Foundation, Stockholm.

REFERENCES

- Adams, AP and Pybus, DA: Delayed respiratory depression after use of fentanyl during anaesthesia.
Br Med J, 1:278, 1978.
- Azar, I and Turndorf, H: Severe hypertension and multiple atrial premature contractions following naloxone administration.
Anesthesia and Analgesia, 58:524, 1979.
- Bengtsson, C, Johnsson, G and Regårdh, C-G: Plasma levels and effects of metoprolol on blood pressure and heart rate in hypertensive patients after an acute dose and between two doses during long-term treatment.
Clin Pharm and Therap, 17:400, 1975.
- Conway, J and Amery, A: The antihypertensive effect of propranolol and other beta-adrenoceptor antagonists.
Central Action of Drugs in the Regulation of Blood Pressure (eds D. Davies and J. Reid). Pitman Medical Publishing Co. Ltd, London, p. 277, 1975.
- Dahlgren, N and Messeter, K: Treatment of stress response to laryngoscopy and intubation with fentanyl.
Anaesthesia, 36:1022, 1981.
- DuBois, D and DuBois, EF: A formula to estimate the approximate surface area if height and weight be known.
Arch Int Med, 17:863, 1916
- Eklund, B, Hjemdahl, P, Seidemann, P and Atterhög, J-H: Effects of prazosin on hemodynamics and sympatho-adrenal activity in hypertensive patients.
J Cardiovascular Pharmacol, 5:184, 1983.
- Eriksson, BM: Aluminium foil instead of glass plates for thin-layer chromatography in radioenzymic assay.
Clin Chem, 27:341, 1981.
- Eriksson, I and Sjöstrand, U: A clinical evaluation of high-frequency positive-pressure ventilation (HFPPV) in laryngoscopy under general anaesthesia.
Acta anaesth scand, suppl 64:101, 1977.

- Ervik, M: Quantitativ determination of metoprolol in plasma and urine by gas chromatography.
Acta pharmacol toxicol (Cph), 36:suppl V, 136, 1975.
- Esler, M, Jackman, G, Leonard, P, Skews, H, Bobik, A and Jennings, G: Effect of propranolol on noradrenaline kinetics in patients with essential hypertension.
Br J Clin Pharmacol, 12:375, 1981.
- Estilo, AE and Cottrell, JE: Naloxone, hypertension, and ruptured cerebral aneurysm. Anesthesiology, 54:352, 1981.
- Evans, JM, Hogg, MIJ, Lunn, JN and Rosen, M: Degree and duration of reversal by naloxone of effects of morphine in conscious subjects.
Br Med J, 2:589, 1974.
- Flacke, JW, Flacke, WE and Williams, GD: Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. Anesthesiology, 47:376, 1977.
- Fox, EJ, Sklar, GS, Hill, CH, Villanueva, R and Ring BD: Complications related to the pressor response to endotracheal intubation. Anesthesiology, 47:524, 1977.
- Gibbons, DO, Lant, AF, Ashford, A, Collins, RF and Pinder, S: Comparative effects of acebutolol and practolol on the lipolytic response to isoprenaline.
Br J Clin Pharmacol, 3:177, 1976.
- Goldman, L and Caldera, DL: Risks of general anesthesia and elective operation in the hypertensive patient. Anesthesiology, 50:285, 1979.
- Grossman, A and Besser M: Opiates control acth through a noradrenergic mechanism.
Clin Endocrinol, 17:287, 1982.
- Haglund, K and Collste, C: Time course of blood pressure, pulse rate, plasma renin and metoprolol during treatment of hypertensive patients.
Eur J Clin Pharmacol, 17:321, 1980
- Hamill, JF, Bedford, RF, Weaver, DC and Colohan, AR: Lidocaine before endotracheal intubation: Intravenous or laryngotracheal?
Anesthesiology, 55:578, 1981.

- Hansson, B-G, Dymling, J-F, Manhem, P and Hökdel, B: Long term treatment of moderate hypertension with the beta¹-receptor blocking agent metoprolol.
Eur J Clin Pharmacol, 11:247, 1977.
- Hjort Sørensen, C, Bredgaard Sørensen, M and Jacobsen, E: Pulmonary hemodynamic during direct diagnostic laryngoscopy.
Acta anaesth scand, 25:51, 1981.
- Laurell, S and Tibbling, G: An enzymatic-fluorimetric micromethod for the determination of glycerol.
Clin Chim Acta, 13:317, 1966.
- Longnecker, DE, Grazis, PA and Eggers, GWN: Naloxone for antagonism of morphine-induced respiratory depression.
Anesthesia and Analgesia, 52:447, 1973.
- Marks, V: An improved glucose oxidase method for determining blood, c.s.f. and urine glucose levels.
Clin Chim Acta, 4:395, 1959
- Martin, DE, Rosenberg, H, Aukburg, SJ, Bartkowski, RR, Edwards, MW, Greenhow, DE and Klinteberg, PL: Low dose fentanyl blunts circulatory responses to tracheal intubation.
Anesthesia and Analgesia, 61:680, 1982
- Martin, WR: Naloxone.
Annals of Internal Medicine, 85:765, 1976.
- Meyer, DR and Sparber, SB: Evidence of possible opiate dependence during the behavioural depressant action of a single dose of morphine.
Life Sci, 21:1087, 1977.
- Michaelis, LL, Hickey, PR, Clark, TA and Dixon, WM: Ventricular irritability associated with the use of naloxone hydrochloride.
Annals of Thoracic Surgery, 18:608, 1974.
- Nicotero, JA, Beamer, V, Moltsos, SE, and Shapiro, AP: Effects of propranolol on the pressor response to noxious stimuli in hypertensive patients.
Am J Cardiol, 22:657, 1968.

- Nutt, JG and Jasomski, DR: Methadone-naloxone mixtures for use in methadone maintenance programs. An evaluation in man of their pharmacological feasibility. II. Demonstration of acute physical dependence.
Clin Pharm and Therap, 15:156, 1974.
- Nyberg, G, Graham, RM and Stokes, GS: The effect of mental arithmetic in normotensive and hypertensive subjects and its modification by beta-adrenergic receptor blockade.
Br J Clin Pharmacol, 4:469, 1977.
- Peuler, J and Johnson, G: Simultaneous single isotope radioenzymic assay of plasma norepinephrine, epinephrine and dopamine.
Life Sci, 21:625, 1977.
- Pontén, J, Biber, B, Henriksson, B-Å, Hjalmarsson, Å, Jonsteg, C and Lundberg, D: Beta-receptor blockade and neurolept anaesthesia. Withdrawal vs continuation of long-term therapy in gall-bladder and carotid artery surgery.
Acta anaesth scand, 26:576, 1982.
- Prys-Roberts, C, Meloche, R and Foëx, P: Studies of anesthesia in relation to hypertension I: Cardiovascular responses of treated and untreated patients.
Br J Anaesth, 43:122, 1971.
- Prys-Roberts, C, Gersh, BJ, Baker, AB and Reuben, SR: The effects of halothane on the interactions between myocardial contractility, aortic impedance, and left ventricular performance. I: Theoretical considerations and results.
Br J Anaesth, 44:634, 1972.
- Prys-Roberts, C, Foëx, P, Biro, GP and Roberts, JG: Studies of anaesthesia in relation to hypertension. V: Adrenergic beta-receptor blockade.
Br J Anaesth, 45:671, 1973.
- Roizen, MF, Horrigan, RW and Frazer, BM: Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision - MAC BAR.
Anesthesiology, 54:390, 1981a.
- Roizen, MF, Hamilton, WK and Sohn, YJ: Treatment of stress-induced increases in pulmonary capillary wedge pressure using volatile anesthetics.
Anesthesiology, 55:446, 1981b.

- Rollason, WN and Russell, JG: Intravenous metoprolol and cardiac dysrhythmias. An evaluation in the management of dysrhythmias in outpatient dental anaesthesia.
Anaesthesia, 35:783, 1980.
- Ryhänen, P, Saarela, E, Saukkonen, J and Hollmén, A: Circulatory responses to laryngoscopy and endotracheal intubation in patients with and without cardiovascular disease. Effect of prophylactic practolol.
Ann Chir Gynaecol, 66:294, 1977.
- Siedlecki, L: Disturbances in the function of cardiovascular system in patients following endotracheal intubation and attempts of their prevention by pharmacological blockade of sympathetic systems.
Anesth Resusc Intens Ther, 3:107, 1975.
- Stanley, TH, Philbin, DM and Coggins, CH: Fentanyl-oxygen anaesthesia for coronary artery surgery: cardiovascular and antidiuretic hormone responses.
Can Anaesth Soc J, 3, 26:168, 1979.
- Stoelting, RK: Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine.
Anesthesiology, 47:381, 1977.
- Taggart, P and Carruthers, M: Suppression by oxprenolol of adrenergic response to stress.
Lancet, 2:256, 1972.
- Tarazi, R.C and Dustan, HP: Beta adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variations.
Am J Cardiol, 29:633, 1972.
- Trimarco, B, Wikstrand, J, Buzzetti, G, Ricciardelli, B, DeLuca, N, Volpe, M and Condorelli, M: Regression of left ventricular hypertrophy and improvement of left ventricular function after long-term antihypertensive treatment with metoprolol.
Abstract, 9th Scientific Meeting of the International Society of Hypertension, Mexico City, 1982.
- Volavka, J, Cho, D, Mallya, A and Bauman, J: Naloxone increases ACTH and cortisol levels in man.
N Engl J Med, 300:1056, 1979.

von Bahr, C, Collste, P, Frisk-Holmberg, M, Haglund, K, Jorfelt, L, Orme, M, Östman, J and Sjöqvist, F: Plasma levels and effects of metoprolol on blood pressure, adrenergic beta receptor blockade, and plasma renin activity in essential hypertension.
Clin Pharm and Therap, 20:130, 1976.

Weigand, H: Über die Narkose bei der Mikrolaryngoskopie und endolaryngealen Mikrochirurgie, II: Das reflektorische Kreislaufverhalten und seine Beeinflussung durch Oberflächenanaesthesia.
Anaesthesist, 19:131, 1970.

Werner, O and Benthin, M: Mean intravascular pressure without tears. Simultaneous recording of the unfiltered pressure curve, and of mean pressure.
Anaesthesia, 37:836, 1982.

William-Olsson, T, Fellenius, E, Björntorp, P and Smith, U: Difference in metabolic responses to beta-adrenergic stimulation after propranolol or metoprolol administration.
Acta med scand, 205:201, 1979.

Wood-Smith, FG, Vickers, MD and Stewart, HC: Drugs in anaesthetics practice.
4th ed. London, Butterworths, 330, 1973.

I.V. PRACTOLOL DURING MICROLARYNGOSCOPY. EFFECT ON ARTERIAL PRESSURE, HEART RATE, BLOOD GLUCOSE AND LIPOLYSIS

O. WERNER, J. MAGNUSSON, R. FLETCHER, P. NILSSON-EHLE AND O. PAHLM

SUMMARY

Twenty-five patients undergoing microlaryngoscopy were anaesthetized with thiopentone and nitrous oxide with suxamethonium as a muscle relaxant. Thirteen received practolol 0.4 mg kg^{-1} and atropine 1.5 mg i.v. shortly before anaesthesia. During anaesthesia practolol 0.2 mg kg^{-1} was given. Twelve (control) received atropine 0.5 mg before anaesthesia. Practolol reduced the frequency of tachycardia and arrhythmia. The treatment group had a greater reduction in systolic arterial pressure during induction. The hypertensive response to laryngoscopy was not significantly attenuated by practolol. A weak hyperglycaemic response to microlaryngoscopy was not affected, nor was the plasma concentration of glycerol.

I.v. β_1 selective adrenoceptor blockade has been tried to combat the circulatory response to laryngoscopy and tracheal intubation. Although there is a good effect in limiting tachycardia and arrhythmia, conflicting results have been obtained in respect of protection against increases in arterial pressure. Prys-Roberts and others (1973) used practolol (Eraldin, I.C.I.) in hypertensive subjects, and found a significant attenuating effect. Similar results were obtained by Ryh nen and others (1977). Siedlecki (1975) found no effect on the hypertensive response. However, different types of anaesthesia were used in those three studies and the assignment of patients to treatment or control groups was, apparently, not strictly randomized.

Microlaryngoscopy causes a similar but more lasting cardiovascular response (Weigand, 1970). We describe a randomized trial on the cardiovascular effects of i.v. practolol during microlaryngoscopy. To test whether the procedure leads to a metabolic stress response and whether this response can be attenuated by practolol, we measured blood-glucose and plasma glycerol concentrations. The latter is considered to be the most sensitive indicator of adipose tissue lipolysis (Havel, 1965).

PATIENTS AND METHODS

Twenty-five patients undergoing microlaryngoscopy were studied. Those with diabetes, obstructive lung

disease, inspiratory difficulties, congestive heart failure, second or third degree A-V block, moderate or severe heart enlargement on chest x-ray were excluded, as were patients receiving digitalis or antihypertensive treatment, including beta-blockers. Informed consent was obtained from the patients.

The patients were fasted from midnight. In the morning, a 12-lead e.c.g. was taken and arterial pressure measured after 10–15 min of rest. A portable e.c.g. recorder (SRA, Sweden) was attached. One lead (modified V_6) was used. The patients were premedicated with morphine and hyoscine i.m. according to age (table I). On arrival at the operating theatre, the patient lay recumbent for 10–15 min, after which blood was sampled through a plastic i.v. cannula. E.c.g. leads were attached for oscilloscope monitoring. Allocation to practolol or saline (control) treatment was random. The anaesthetist, but not the person measuring arterial pressure, knew the nature of the treatment given. Immediately before injections systolic arterial pressure was measured by radial artery palpation. The same cuff (width 12 cm) and aneroid manometer were used for all patients. The manometer had been checked against a mercury manometer and been found to be correct within 4 mm Hg in the range 0–260 mm Hg. All patients were first given atropine sulphate 0.5 mg i.v. so that the heart rate response would not reveal which drugs were given subsequently. Thereafter, either saline (controls) or atropine 1.0 mg (treatment group) was given. Practolol 0.4 mg kg^{-1} or saline was administered during 4 min, starting 1 min after the injection of atropine. Two minutes later, thiopentone was

O. WERNER, M.D.; J. MAGNUSSON, M.D.; R. FLETCHER, F.F.A.R.C.S.; Department of Anaesthesia. P. NILSSON-EHLE, M.D., Department of Clinical Chemistry. O. PAHLM, M.D., Department of Clinical Physiology. University Hospital of Lund, S-221 85 Lund, Sweden.

0007-0912/80/010091-06 \$01.00

© Macmillan Journals Ltd 1980

TABLE I. Some comparisons of the two groups. Values are given as mean $\pm$ 1 SD (when applicable). ML = microlaryngoscopy

	Treatment	Control
Males/females	13/0	11/1
Age (yr)	58 $\pm$ 12	50 $\pm$ 16
Weight (kg)	77 $\pm$ 12	78 $\pm$ 17
Resting arterial pressure (mm Hg)		
Systolic	139 $\pm$ 16	135 $\pm$ 24
Diastolic	77 $\pm$ 9	80 $\pm$ 11
Heart rate at rest (beat min ⁻¹)	66 $\pm$ 9	59 $\pm$ 10
Premedication		
Morphine (mg)	8.4 $\pm$ 3.1	9.3 $\pm$ 3.8*
Hyoscine (mg)	0.34 $\pm$ 0.12	0.37 $\pm$ 0.12
Induction		
Thiopentone (mg kg ⁻¹)	4.2 $\pm$ 0.4	4.7 $\pm$ 0.6
Suxamethonium (mg kg ⁻¹)	1.1 $\pm$ 0.2	1.1 $\pm$ 0.2
Time intervals (min)		
Premedication-anaesthesia	75 $\pm$ 34	78 $\pm$ 25
Induction-intubation	2.8 $\pm$ 0.6	2.9 $\pm$ 0.6
Intubation-start of ML	5 $\pm$ 2	5 $\pm$ 2
Start-end of ML	14 $\pm$ 10	14 $\pm$ 7
End of ML-extubation	5 $\pm$ 4	6 $\pm$ 4
Subjects receiving fentanyl	3	4
Mean dose of fentanyl in these subjects (mg)	0.12	0.15

* One subject received diazepam 5 mg i.m. instead.

injected over approximately 1 min, followed by suxamethonium. The lungs were ventilated with 5–10 breaths of oxygen, after which the trachea was intubated with the aid of a Macintosh laryngoscope. The tube (cuffed Portex 6.5) was lubricated with tetracaine gel; otherwise, no topical anaesthesia was given. Subsequently, the lungs were ventilated manually with nitrous oxide 70% in oxygen. A suxamethonium infusion (2 mg ml⁻¹ in Ringer solution) was started when the patient showed signs of recovering from the initial paralysis. During the induction of anaesthesia systolic arterial pressure was measured and recorded every 30–45 s. Thereafter arterial pressure was measured every minute throughout the procedure. No fentanyl was given before or during induction. During microlaryngoscopy fentanyl 0.1 mg was given if the systolic pressure was 200 mm Hg or greater, for at least 2 min. A further 0.1 mg was given if arterial pressure was greater than 225 mm Hg. Practolol 0.2 mg kg⁻¹ or saline was given slowly between 12 and 14 min after the end of the first injection, about 10–12 min after the start of anaesthesia. Blood was sampled 20 min after the start of anaesthesia. The arterial pressure measurements continued at 1-min intervals until 2 min after extubation.

Analyses. Electrocardiograph tapes were replayed on a computer system (Pahlm et al., 1978). Significant events, such as injections, were identified with a marker pulse. An e.c.g. record covering the whole procedure was written on paper (25 mm s⁻¹). Arrhythmia was evaluated from the e.c.g. record by an observer who was unaware of the treatment. Heart rate was measured from e.c.g. every 20 s beginning 1 min before the injection of atropine. The blood samples were immediately placed in ice. Samples for analysis of blood-glucose were drawn in tubes containing sodium fluoride and analysed within 6 h by an enzymatic-colorimetric method (Marks, 1959). Blood samples for glycerol analysis were drawn in tubes containing EDTA. Plasma was separated by centrifugation immediately after operation, and stored at -20 °C. Glycerol concentrations were measured by an enzymatic-fluorimetric method (Laurell and Tibblin, 1966).

Statistics. The Mann-Whitney (two-sided) rank sum test for unpaired data was used for between-group comparisons. The Wilcoxon (two-sided) rank sum test for paired data was used for within-group comparisons. Probability values <0.05 were considered to indicate statistical significance.

RESULTS

There were no notable differences between the groups in respect of resting arterial pressure, weight, premedication, anaesthetic drugs given and duration of the procedure, except that the controls received slightly more thiopentone (table I).

Systolic arterial pressure. Mean arterial pressure at rest immediately before injection of atropine was similar in the two groups. Compared with the initial pressure, no significant change in systolic arterial pressure occurred during or after the first injection of practolol or saline in either group. Minimum arterial pressure during induction was less in the practolol group ($P < 0.05$) (fig. 1). Maximum arterial pressure within 2 min after laryngoscopy and intubation was greatest in the control group. However, a large increase in arterial pressure occurred in the treatment group, so that the difference between groups was not statistically significant. Usually the arterial pressure decreased during the few minutes before microlaryngoscopy, but when microlaryngoscopy began, arterial pressure increased, remaining increased in both groups during the rest of the procedure, and also after repeated injection of saline or practolol 0.2 mg kg⁻¹.

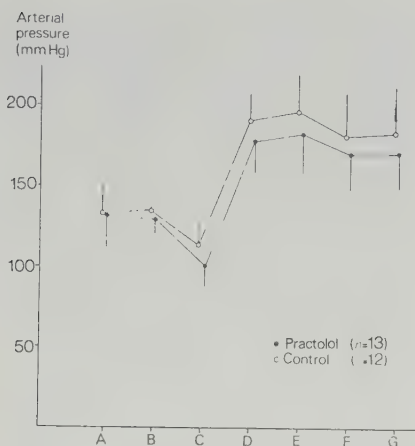


FIG. 1. Systolic arterial pressure before and during microlaryngoscopy (group mean and 1 SD). A = Immediately before injections; B = 1 min after injection of atropine and practolol (saline). Patient still awake; C = smallest value recorded during induction (this always occurred before intubation); D = greatest value within 2 min after laryngoscopy and intubation; E = greatest value during microlaryngoscopy; F = mean value during microlaryngoscopy; G = 2 min after repeated injection of practolol 0.2 mg kg^{-1} or saline. SD in panel A was calculated directly from the recorded values, while panels B-G show the standard deviation of the change in relation to A.

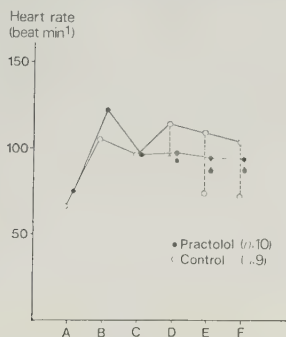


FIG. 2. Heart rate (group means): A = before injections; B = maximum after atropine; C = 1 min after practolol; D = maximum/minimum during induction; E = maximum/minimum during diagnostic laryngoscopy; F = maximum/minimum during awakening.

Heart rate. The tape recording failed for various technical reasons in three subjects of each group. In the remaining subjects, no significant differences between groups were found immediately before atropine (fig. 2). Compared with the initial heart rate, the increase after atropine was greater in the treatment group (who received 1.5 mg) than in the other group (0.5 mg), although the difference was not significant. The heart rate decreased more after practolol than after saline, so that heart rates were again nearly equal 1 min after practolol or saline injection. Induction of anaesthesia and intubation caused very little response in the treatment group, while the maximum heart rate in the other group was significantly greater in relation to the initial heart rate ($P < 0.01$). The controls also had significantly greater maximum heart rates during microlaryngoscopy ($P < 0.01$) and during awakening and extubation ($P < 0.05$) and there was greater variation in heart rate during the procedure (fig. 2).

Arrhythmia. Among 10 e.c.g. tapes from the practolol group, one showed a total of three ventricular extrasystoles during and shortly after injection of practolol. Otherwise, no arrhythmia was seen except sinus tachycardia in some cases.

Among nine tapes from the controls, three showed junctional rhythm during intubation, while other disturbances of rhythm were observed shortly after atropine in two patients (marked sinus arrhythmia and ventricular extrasystoles respectively). One patient already had ventricular extrasystoles before atropine. These persisted and increased in number during microlaryngoscopy.

Blood-glucose and plasma glycerol. Blood-glucose increased slightly during anaesthesia in both groups (table II). The increase was significant only in the practolol group ($P < 0.05$). The difference in blood-glucose between the groups was not significant. The initial mean plasma glycerol concentrations were slightly greater than the upper reference limit ($100 \mu\text{mol litre}^{-1}$). In the control group, plasma

TABLE II. Mean blood-glucose and plasma glycerol concentrations before and during anaesthesia. Numbers within parentheses show SD of the initial value/SD of the change

	Treatment		Control	
	Before	During	Before	During
Blood-glucose (mmol litre^{-1})	5.6 (0.7)	6.0 (0.7)	5.5 (1.3)	5.7 (0.7)
Plasma glycerol ($\mu\text{mol litre}^{-1}$)	122 (46)	114 (48)	144 (63)	151 (49)

glycerol concentrations increased slightly during microlaryngoscopy; in the practolol group there was a small decrease in mean glycerol concentration. The difference in response between the two groups, was not statistically significant (table II).

DISCUSSION

Heart rate and contractility are stimulated via beta adrenoceptors, mainly β_1 (Carlsson et al., 1977). The degree of blockade of cardiac beta adrenoceptors appears to be closely related to the plasma concentration of the beta blocker (Vaughan Williams et al., 1975). The relation between plasma concentration and antihypertensive effect is less direct. Thus, a single dose of beta blocker does not greatly reduce arterial pressure (Tarazi and Dustan, 1972). The full effect is seen only after a few hours or days of treatment (Conway and Amery, 1975). Likewise, a single dose suppresses the tachycardia associated with mental stress, but has little effect on the hypertensive response (Nyberg, Graham and Stokes, 1977). The same applies to the effects of beta blockers on the circulatory response to isometric exercise (Sangvik et al., 1975) and to the effects during direct stimulation of the defense-alarm area of the dog brain (Åblad et al., 1975). Thus, except for dynamic exercise, short-term administration of beta blockers does not greatly attenuate the hypertensive response associated with many types of stress. However, they do reduce heart rate.

Since acute administration is rather ineffective in the awake subject, it is far from evident that beta blockers are effective antihypertensive agents during anaesthesia. One thing is to be expected, namely interaction between the beta blocker, external stimuli and the anaesthetic, which always exerts its own effects on the cardiovascular system. The present findings support this concept. The greater decrease in systolic arterial pressure during induction in the treatment group may be explained by such interaction. Thiopentone seems to cause a pooling of blood in the systemic capacitance vessels, by depression of medullary centres. This reduces cardiac output and, usually, arterial pressure (Conway and Ellis, 1969). An additional effect of practolol, further reducing cardiac output and arterial pressure, is likely. During laryngoscopy and intubation, the central depressant action of thiopentone is strongly counteracted. This may explain why practolol did not significantly attenuate the hypertensive response—paralleling the lack of effect of beta blockers in awake subjects under stress.

Carruthers and others (1974) showed a rapid reduction in plasma concentration of practolol after i.v. injection. This is not an explanation for the lack of significant antihypertensive effect during intubation or microlaryngoscopy. In both cases, plasma concentrations were obviously great enough to inhibit tachycardia. Also, the arterial pressure was not much less among those treated than among those not treated 2 min after a repeated injection of practolol (saline).

We followed the recommendation of Prys-Roberts and others (1973), to give a generous dose of atropine before practolol in order to avoid bradycardia. We do not believe that practolol without atropine would have been more effective against the hypertensive response, although heart rates would, of course, have been slower. Our belief is based on the studies cited in the first paragraph of this discussion. As mentioned, acute beta blockade (without atropine) reduced stress-induced tachycardia, but had little effect on the hypertensive response.

The present results agree with those of Siedlecki (1975), who used the same type of induction and did not find any attenuation by practolol of the arterial pressure response to intubation. Superficially, the results contradict those of Prys-Roberts and others (1973), who studied hypertensive subjects intubated under halothane-nitrous oxide anaesthesia, and those of Ryhänen and others (1977), who used thiopentone combined with halothane-nitrous oxide in a mixed group of normo- and hypertensive patients. They found that i.v. practolol did reduce the arterial pressure response to laryngoscopy and intubation. We believe that the discrepancy may be explained by the type of anaesthesia used. Thus, halothane has potent cardiovascular effects, particularly as a myocardial depressant (Prys-Roberts et al., 1972). Practolol may have potentiated the effect of halothane. This explanation may seem difficult to reconcile with the findings by Slogoff and others (1977) who found, in experiments on dogs under isoprenaline challenge, that halothane does not potentiate the haemodynamic effects of propranolol. Also propranolol actually *increased* the mean aortic pressure in these experiments, although cardiac output decreased. However, the beta stimulation by isoprenaline is probably not analogous to the sympathetic stimulation caused by laryngoscopy. Furthermore, propranolol is non-selective and therefore counteracts the systemic vasodilator effects of β_2 stimulation.

Our conclusions are that beta blockade, instituted shortly before or during anaesthesia, does not

effectively counteract the hypertensive response to laryngoscopy, unless other agents are also given which are potentiated by the beta blocker. Deep general anaesthesia (King et al., 1951) or thorough topical analgesia (Stoelting, 1977) would seem to give more predictable effects. In order to reduce the hypertensive response to microlaryngoscopy, we prefer to complement thiopentone-nitrous oxide anaesthesia with fentanyl 0.2–0.5 mg and to give naloxone after the procedure, if necessary. This seems to reduce the arterial pressure response. At the time of these studies, however, the practice at our hospital was to use fentanyl sparingly and it was used about equally often in both groups (table I). The comparison between the groups ought not to have been affected, therefore.

In contrast to its effect on hypertension, a single dose of beta blocker is certainly effective against tachycardia during anaesthesia and operation. This was the case in the present study and several previous ones (Ryder, Charlton and Gorman, 1973). The effect on stress-induced arrhythmia is also striking (Katz and Bigger, 1970). However, for the latter purpose, much smaller doses are needed than those employed in the present study.

Non-selective beta blockade has been shown to attenuate the hyperglycaemic and lipolytic response to stress (Taggart and Carruthers, 1972). In the present study, a weak hyperglycaemic response to microlaryngoscopy was obtained, which was not affected by practolol. Perhaps surprisingly, the procedure had no significant effect on plasma glycerol concentrations. Also, there was no significant difference in lipolytic response between the groups. The last result is consistent with the observations of Gibbons and others (1976), who found that practolol does not affect the basal level of lipolysis, but has a weak inhibitory effect on isoprenaline-induced lipolysis.

ACKNOWLEDGEMENT

We thank Drs N. Dahlgren and K. Messeter for showing us their data on pretreatment with fentanyl before intubation.

REFERENCES

- Ablad, B., Carlsson, E., Dahlöf, C., and Ek, L. (1975). Some aspects on the pharmacology of adrenergic β -receptor blockers; in *Pathophysiology and Management of Arterial Hypertension* (eds G. Berglund, L. Hansson and L. Werkö), p. 152. Mölndal, Sweden: A. Lindgren & Söner.
- Carlsson, E., Dahlöf, C.-G., Hedberg, A., Persson, H., and Tångstrand, B. (1977). Differentiation of cardiac chronotropic and inotropic effects of 8-adrenoceptor agonists. *Naunyn Schmiedeberg's Arch. Pharmacol.*, **300**, 101.
- Carruthers, S. G., Kelly, J. G., McDevitt, D. G., and Shanks, R. G. (1974). Blood levels of practolol after oral and parenteral administration and their relationship to exercise heart rate. *Clin. Pharmacol. Ther.*, **15**, 497.
- Conway, C. M., and Ellis, D. B. (1969). The haemodynamic effects of short-acting barbiturates. *Br. J. Anaesth.*, **41**, 534.
- Conway, J., and Amery, A. (1975). The antihypertensive effect of propranolol and other β -adrenoceptor antagonists; in *Central Action of Drugs in the Regulation of Blood Pressure* (eds D. Davies and J. Reid), p. 277. London: Pitman Medical Publishing Co. Ltd.
- Gibbons, D. O., Lant, A. F., Ashford, A., Collins, R. F., and Pinder, S. (1976). Comparative effects of acebutolol and practolol on the lipolytic response to isoprenaline. *Br. J. Clin. Pharmacol.*, **3**, 177.
- Havel, R. J. (1965). Some influences of the sympathetic nervous system and insulin on the mobilization of fat from adipose tissue: studies of the turnover rates of free fatty acid and glycerol. *Ann. N.Y. Acad. Sci.*, **131**, 91.
- Katz, R. L., and Bigger, J. T. (1970). Cardiac arrhythmias during anaesthesia and operation. *Anesthesiology*, **33**, 193.
- King, B. D., Harris, L. C., Greifenstein, F. E., Elder, J. D., and Dripps, R. D. (1951). Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anaesthesia. *Anesthesiology*, **12**, 556.
- Laurell, S., and Tibbling, G. (1966). An enzymatic-fluorimetric micromethod for the determination of glycerol. *Clin. Chim. Acta*, **13**, 317.
- Marks, V. (1959). An improved glucose oxidase method for determining blood, c.s.f. and urine glucose levels. *Clin. Chim. Acta*, **4**, 395.
- Nyberg, G., Graham, R. M., and Stokes, G. S. (1977). The effect of mental arithmetic in normotensive and hypertensive subjects, and its modification by β -adrenergic receptor blockade. *Br. J. Clin. Pharmacol.*, **4**, 469.
- Pahlm, O., Börjesson, P. O., Johansson, K., Jonson, B., Petersson, K., Sörnmo, L., and Werner, O. (1978). Efficient data compression and arrhythmia detection for long-term e.c.g.s; in *Proc. "Computers in Cardiology 1978"*. IEEE, Inc.
- Prys-Roberts, C., Foëx, P., Biro, G. P., and Roberts, J. G. (1973). Studies of anaesthesia in relation to hypertension. V: Adrenergic beta-receptor blockade. *Br. J. Anaesth.*, **45**, 671.
- Gersh, B. J., Baker, A. B., and Reuben, S. R. (1972). The effects of halothane on the interactions between myocardial contractility, aortic impedance, and left ventricular performance. I: Theoretical considerations and results. *Br. J. Anaesth.*, **44**, 634.
- Ryder, W., Charlton, J. E., and Gorman, P. B. W. (1973). Oral atropine and practolol premedication in dental anaesthesia. *Br. J. Anaesth.*, **45**, 745.
- Ryhänen, P., Saarela, E., Saukkonen, J., and Hollmén, A. (1977). Circulatory responses to laryngoscopy and endotracheal intubation in patients with and without cardiovascular disease. Effect of prophylactic practolol. *Ann. Chir. Gynaecol.*, **66**, 294.

- Sangvik, K., Stokkeland, M., Lindseth-Ditlefsen, E.-M., and Nyberg, G. (1975). Circulation reaction at rest and during isometric and dynamic exercise in hypertensive patients: influence of different adrenergic beta-adrenoceptor antagonists. *Pharmotherapeutica*, **1**, 71.
- Siedlecki, J. (1975). Disturbances in the function of cardiovascular system in patients following endotracheal intubation and attempts of their prevention by pharmacological blockade of sympathetic system. *Anaesth. Resus. Inten. Ther.*, **3**, 107.
- Slogoff, S., Keats, A. S., Hibbs, C. W., Edmonds, C. H., and Bragg, D. A. (1977). Failure of general anesthesia to potentiate propranolol activity. *Anesthesiology*, **47**, 504.
- Stoelting, R. K. (1977). Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology*, **47**, 381.
- Taggart, P., and Carruthers, M. (1972). Suppression by oxprenolol of adrenergic response to stress. *Lancet*, **2**, 256.
- Tarazi, R. C., and Dustan, H. P. (1972). Beta adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variations. *Am. J. Cardiol.*, **29**, 633.
- Vaughan Williams, E. M., Raine, A. E. G., Cabrera, A. A., and Whyte, J. M. (1975). The effects of prolonged β -adrenoceptor blockade on heart weight and cardiac intracellular potentials in rabbits. *Cardiovasc. Res.*, **9**, 579.
- Weigand, H. (1970). Über die Narkose bei der Mikrolaryngoskopie und endolaryngealen Mikrochirurgie. II: Das reflektorische Kreislaufverhalten und seine Beeinflussung durch Oberflächenanaesthetica. *Anaesthesist*, **19**, 131.
- INJECTION INTRA-VEINEUSE DE PRACTOLOL PENDANT UNE MICROLARYNGOSCOPIE. EFFET SUR LA PRESSION ARTERIELLE, LA FREQUENCE CARDIAQUE, LA GLUCOSE DU SANG ET LA LIPOLYSE
- RESUME
- Vingt-cinq patients soumis à une microlaryngoscopie ont été anesthésiés au thiopentone et au protoxyde d'azote, auxquels on a ajouté un agent de relaxation des muscles: le Suxaméthonium. Treize patients ont reçu du practolol à raison de 0,4 mg kg⁻¹ et de l'atropine à raison de 1,5 mg peu avant l'anesthésie. Pendant l'anesthésie, on leur a administré du practolol à raison de 0,2 mg kg⁻¹. Douze témoins ont reçu 0,5 mg d'atropine avant l'anesthésie. Le practolol a réduit la fréquence de la tachycardie et de l'arythmie. La pression artérielle systolique a été considérablement réduite pendant l'induction chez le groupe soumis au traitement. Le practolol n'a pas atténué de façon significative la réaction hypertensive à la laryngoscopie. Une faible hyperglycémie due à la microlaryngoscopie n'a pas été affectée et il en a été de même pour la concentration de glycérol dans le plasma.
- PRACTOLOL INTRAVENÖS WÄHREND MICROLARYNGOSKOPIE. AUSWIRKUNG AUF ARTERIELLEN DRUCK, PULSZAHL, BLUTZUCKER UND LIPOLYSE
- ZUSAMMENFASSUNG
- Fünfundzwanzig Patienten wurden für Mikrolaryngoskopie mit Thiopenton und mit Stickoxyd mit Suxamethonium als Muskelentspannungsmittel narkotisiert. Dreizehn davon erhielten kurz vor der Narkose 0,4 mg kg⁻¹ Practolol und intravenös 1,5 mg Atropin. Während der Narkose wurden 0,2 mg kg⁻¹ Practolol verabreicht. Zwölf Kontrollpatienten erhielten vor der Narkose 0,5 mg Atropin. Durch Practolol wurde die Häufigkeit von Tachykardie und Arrhythmie verringert. Die Behandlungsgruppe zeigte eine grössere Verringerung des systolischen arteriellen Druckes während Narkoseeinleitung. Die hypertensive Reaktion auf Laryngoskopie wurde durch Practolol nicht wesentlich erhöht. Eine schwache Hyperglykämische Reaktion auf Mikrolaryngoskopie wurde nicht beeinträchtigt, auch nicht die Plasmakonzentration von Glyzerol.
- PRACTOLOL I.V. DURANTE MICROLARYNGOSCOPIA. EFECTO SOBRE LA PRESION ARTERIAL, EL RITMO CARDIACO, LA GLUCOSA SANGUINEA Y LA LIPOLISIS
- SUMARIO
- A 25 pacientes sometidos a microlaringoscopia, se les administró tiopentona y óxido nítrico junto con suxametonio como relajante muscular. Trece recibieron 0,4 mg kg⁻¹ de practolol y 1,5 mg de atropina i.v. poco antes de la anestesia. Se administró 0,2 mg kg⁻¹ de practolol durante la anestesia. Doce (controles) recibieron 0,5 mg de atropina antes de la anestesia. El practolol redujo la frecuencia de la taquicardia y de la arritmia. El grupo tratado experimentó una mayor reducción de la presión arterial sistólica durante la inducción. El practolol no atenuó significativamente la respuesta hipertensiva a la laringoscopia. No hubo efecto en la respuesta hiperglicémica débil a la microlaringoscopia ni tampoco en la concentración de glicerol en el plasma.

METOPROLOL, FENTANYL AND STRESS RESPONSES TO MICROLARYNGOSCOPY

Effects on arterial pressure, heart rate and plasma concentrations of catecholamines, ACTH and cortisol

J. MAGNUSSON, O. WERNER, C. CARLSSON, N. NORDÉN
AND K.-I. PETTERSSON

SUMMARY

Forty patients undergoing microlaryngoscopy were anaesthetized with thiopentone and nitrous oxide. Twenty patients received metoprolol 200 mg in a slow-release tablet once daily for 4 days up to, and including, the morning of operation, and 10 mg i.v. shortly before induction of anaesthesia. The other patients received placebo tablets and physiological saline i.v., instead. Both groups of 20 patients were further subdivided, half of the patients receiving fentanyl 1.0–1.5 mg during anaesthesia, the effect of which was antagonized by naloxone at the end of the procedure. The other patients received saline i.v. instead of fentanyl or naloxone. Metoprolol decreased heart rate and the general level of arterial pressure during anaesthesia, but did not affect the fluctuations in pressure. Arterial plasma noradrenaline concentrations during microlaryngoscopy were enhanced by metoprolol, in comparison with placebo, the reverse being the case for cortisol concentrations. Fentanyl decreased arterial pressure and plasma ACTH and cortisol concentrations regardless of whether the patient had received metoprolol. Plasma adrenaline and noradrenaline concentrations were decreased by fentanyl in the patients receiving metoprolol.

Although β -adrenoceptor antagonists decrease the occurrence of arrhythmia and tachycardia caused by stressful stimuli during anaesthesia (Rollason and Russell, 1980), their effect on acute alterations in arterial pressure is less clear. For instance, the hypertensive response to laryngoscopy and intubation was not decreased appreciably by practolol i.v. shortly before the induction of anaesthesia with thiopentone (Siedlecki, 1975; Werner et al., 1980).

In a previous study Werner and colleagues (1980) noted that practolol i.v. did not decrease significantly the hypertensive response to microlaryngoscopy, a response that may be pronounced even in subjects who are normotensive before anaesthesia (Weigand, 1970). The full antihypertensive effect of β -blockers is seen only after hours, or days, of treatment (Conway and Amery, 1975) and this suggests that the effects on arterial pressure during anaesthesia, after several days of pretreatment with β -blockers by mouth, may be different from those seen after acute administration i.v. The present paper describes a randomized investigation of the effects of 4 days pretreatment with a β -blocking drug before anaes-

thesia for microlaryngoscopy. The cardioselective β -blocker metoprolol was used and, in order to study the interactions between metoprolol, opiate analgesia and stress, half of the patients received fentanyl also.

PATIENTS AND METHODS

The investigation was approved by the local Human Study Committee. Forty patients, aged 39–79 yr, undergoing microlaryngoscopy were studied. None had received antihypertensive or antiarrhythmic drugs (diuretics, β -blocking drugs or digitalis) previously. Each patient was examined by one of the authors 3 days before anaesthesia, at which time informed consent was obtained and arterial pressure measured by upper arm sphygmomanometry. Patients were then divided in four groups ($n=10$) by stratified randomization according to the value of their systolic arterial pressure (150 mm Hg or less, or greater than 150 mm Hg). Stratification was abandoned in the last few patients to achieve equal numbers in the groups. The groups were:

(I) Controls. These patients received thiopentone and nitrous oxide only.

(II) Patients in this group received thiopentone and nitrous oxide as in group I. In addition, they re-

J. MAGNUSSON, M.D., O. WERNER, M.D., C. CARLSSON, M.D. (Department of Anaesthesia); N. NORDÉN (Department of Clinical Chemistry); K.-I. PETTERSSON (Department of Ear, Nose and Throat Surgery); University of Lund, S-221 85 Lund, Sweden.

ceived fentanyl i.v. shortly before microlaryngoscopy and naloxone following surgery.

(III) Patients in this group received metoprolol 200 mg, in a slow release form, once daily for 4 days. The first tablet was given in the afternoon shortly after the patient had been examined and the last tablet at 6 a.m. on the day of operation. An additional 10 mg was given i.v. 1–3 min before anaesthesia. The techniques of anaesthesia was as in group I.

(IV) Patients in this group received metoprolol (as group III). However, the technique of anaesthesia was the same as in group II (thiopentone, nitrous oxide and fentanyl followed by naloxone).

Assignment to the different groups was double-blind. Thus, patients not given metoprolol (groups I and II) received placebo tablets and received physiological saline i.v. instead of metoprolol before anaesthesia. Patients not given fentanyl and naloxone received equivalent volumes of physiological saline i.v. However, the nature of the treatment could often be deduced from the response of the patient during anaesthesia.

Microlaryngoscopy was performed usually between 1 and 3 p.m. Patients were premedicated with morphine and hyoscine according to age (table I). A cannula was inserted in the radial artery 10–30 min before the induction of anaesthesia and arterial pressure was measured continuously (HP 1280 C transducer (Hewlett Packard)) and displayed with the ECG on a Mingograph 81 recorder (Siemens-Elema). The transducer was calibrated each day

against a water column corresponding to 100 mm Hg. Since the day-to-day variations were small, calibration over the full range (0–300 mm Hg) was performed only once.

Atropine 1.0 mg was administered 4 min before the induction of anaesthesia, and then followed by metoprolol 10 mg, or saline. Anaesthesia was induced with thiopentone. Suxamethonium was administered and the lungs ventilated, using a face-mask, with 5–10 breaths of 100% oxygen, after which tracheal intubation was accomplished with the aid of a Macintosh laryngoscope. This was held in place so that the vocal cords were visualized for 30 s. A Portex 6.5-mm endotracheal tube was lubricated with amethocaine gel, otherwise no topical anaesthesia was given. Subsequently, the lungs were ventilated manually with 70% nitrous oxide in oxygen. Fentanyl 1.0 mg, or saline, was injected in divided doses starting about 5 min after the intubation of the trachea, that is, about 8 min before microlaryngoscopy with the Kleinsasser instrument. Additional fentanyl 0.5 mg, or saline, was given after 20 min of microlaryngoscopy if required. An infusion of suxamethonium ensured adequate muscle relaxation during microlaryngoscopy. Naloxone hydrochloride 0.4 mg i.v. and 0.4 mg s.c., or saline, was injected some 2–4 min after the end of the microlaryngoscopy. The tracheal tube was removed about 5 min later, when adequate spontaneous breathing was established.

Mean arterial pressure (MAP), at rest, 3 days before anaesthesia was calculated as: systolic

TABLE I. Comparisons between the groups. Values are mean $\pm$ 1SD, when applicable, except time intervals which are given as median and (range). ML = Microlaryngoscopy. *One patient received diazepam 10 mg i.m. instead

	Group			
	I	II	III	IV
Males/females	9/1	8/2	8/2	6/4
Age (yr)	65 $\pm$ 11	61 $\pm$ 13	56 $\pm$ 10	56 $\pm$ 11
Weight (kg)	80 $\pm$ 21	71 $\pm$ 12	75 $\pm$ 17	74 $\pm$ 13
Premedication (mg)				
Morphine	6.5 $\pm$ 3.2	6.3 $\pm$ 2.9	7.2 $\pm$ 2.9*	8.0 $\pm$ 3.5
Hyoscine	0.26 $\pm$ 0.12	0.25 $\pm$ 0.12	0.29 $\pm$ 0.12	0.32 $\pm$ 0.12
Anaesthetic drugs (mg kg ⁻¹)				
Thiopentone	4.3 $\pm$ 0.7	4.4 $\pm$ 0.8	4.4 $\pm$ 0.4	4.2 $\pm$ 0.5
Suxamethonium, initial	1.0 $\pm$ 0.2	1.0 $\pm$ 0.1	1.1 $\pm$ 0.1	1.1 $\pm$ 0.1
Suxamethonium, maintenance	5.3 $\pm$ 3.1	2.9 $\pm$ 2.1	4.8 $\pm$ 1.8	1.8 $\pm$ 1.1
Time intervals (min)				
Premedication–anaesthesia	86 (40–280)	94 (55–120)	88 (60–127)	90 (35–110)
Induction–intubation	3.0 (2.5–3.3)	3.0 (1.8–4.5)	2.5 (2.5–4.3)	2.5 (2.3–4.0)
Start–end of ML	7 (6–12)	8 (5–25)	8 (3–26)	12 (8–19)

pressure $\times 1/3$ + diastolic pressure $\times 2/3$. On all other occasions MAP was obtained from the arterial pressure tracing. Values for systolic arterial pressure (SAP) were also noted. However, it was realized that, on occasions, the pressure tracing from the radial artery was distorted. Heart rate was assessed from the ECG. The observer was not informed of the nature of the treatment.

Blood samples were withdrawn from the arterial cannula into prechilled test tubes and immediately immersed in ice-cold water. Plasma was separated within 20 min by 3 min of centrifugation, and stored at -70°C until assay. Samples for noradrenaline and adrenaline assay were withdrawn in tubes containing EGTA and glutathione. A radioenzymatic assay was used (Peuler and Johnson, 1977), slightly modified according to Eriksson (1981). The within-sample coefficient of variation for the assay was 5–7% for adrenaline, and 4–6% for noradrenaline, depending on concentration. The corresponding figure, between samples, was about 10% for both substances. The detection limit was $0.1\text{ nmol litre}^{-1}$ for adrenaline and $0.2\text{ nmol litre}^{-1}$ for noradrenaline. The normal range for arterial plasma concentrations in resting subjects was $0\text{--}0.4\text{ nmol litre}^{-1}$ for adrenaline and $0.8\text{--}2\text{ nmol litre}^{-1}$ for noradrenaline (P. Hjemdahl, personal communication). Recovery of catecholamines with the assay used has been stated to be 65–85% (Peuler and Johnson, 1977). Samples for assay of adrenocorticotropin (ACTH), and cortisol were collected in tubes containing EDTA. A radioimmunoassay (CIS-Sorin, France) was used for the measurement of ACTH concentration. The coefficient of variation between-samples was 17% for concentrations $<50\text{ ng litre}^{-1}$ and 10% for concentrations $>50\text{ ng litre}^{-1}$ with a lower limit of detection at 10 ng litre^{-1} . The upper normal limit at 8 a.m. was 90 ng litre^{-1} (Hedner, Nordén and Valdemarsson, 1981). A solid phase radioimmunoassay was used to measure the plasma cortisol concentration (Clinical Assay, Mass., USA). The between-sample coefficient of variation was 11%. The normal values at 8 a.m. were $280\text{--}830\text{ nmol litre}^{-1}$. Samples for metoprolol assay were collected in test tubes containing sodium heparin and analysed as described by Ervik (1975).

Samples were obtained on four occasions: (a) 5–15 min before the induction of anaesthesia; (b) during undisturbed anaesthesia—just before microlaryngoscopy; (c) after 15 min of microlaryngoscopy or, if the investigation had been com-

pleted by that time, at the end of microlaryngoscopy, and (d) 2–4 min after extubation of the trachea.

Statistics. The Mann-Whitney (two-sided) rank sum test for unpaired data was used for between-group comparisons. Changes in heart rate and arterial pressure in relation to resting values in the untreated patient were compared rather than the directly recorded values. This was in order to decrease the effects of interindividual variation. In contrast, absolute values for plasma concentrations were compared, since no control value was available in the untreated patient. Groups I and II (both receiving placebo) were treated as a single group until fentanyl was given. This group was compared with groups III and IV (both receiving metoprolol), similarly combined. The following between-group comparisons were made after fentanyl: I–II, I–III, II–IV, III–IV. The significance of changes within groups was analysed with the Wilcoxon (two-sided) rank sum test for paired data.

Probability values less than 0.05 (indicated * in tables) were considered to indicate statistical significance. Values less than 0.01 are indicated **.

RESULTS

The groups were similar in respect of age, sex, weight, drugs given and the duration of the procedure, except that patients given fentanyl (groups II and IV) required less suxamethonium during the microlaryngoscopy (table I).

Mean arterial pressure (MAP). Group means were similar in the resting patient before metoprolol or placebo (table II). Before anaesthesia, average MAP was 14 mm Hg less among those given metoprolol, than among the others (n.s.). The difference in mean values for minimum MAP during induction was 16 mm Hg ($P < 0.05$). The average value for maximum MAP at laryngoscopy and intubation was 29 mm Hg less in patients given metoprolol (groups III and IV) than among the others ($P < 0.01$).

Immediately before the microlaryngoscopy, with the patient still undisturbed, MAP was 37 mm Hg less ($P < 0.01$) among patients receiving metoprolol, but not fentanyl (group III), than among the controls (group I). The difference between these groups during microlaryngoscopy, was 21 mm Hg (n.s., table II). Group means for MAP after extubation of the trachea were $10\text{--}23\text{ mm Hg}$ less among patients given metoprolol, than among the others (table II).

TABLE II. Mean arterial pressure (mm Hg) (group means $\pm$ 1SD). Values in the third column are minimum values observed after thiopentone injection, but before intubation, while the fourth column shows maximum values within 3 min after intubation. Values in the sixth column were obtained after 10 min of microlaryngoscopy (ML), or 2 min before the end of microlaryngoscopy, whichever came first. Statistical differences between groups are indicated. * $P < 0.05$; ** $P < 0.01$. Thus, there was a significant difference between groups I and II immediately before and during microlaryngoscopy ($P < 0.01$), but no significant difference on the other occasions. The significance of changes within groups was not assessed

Group		Rest, untreated	5 min before anaesth.	Min. at induction	Max. at intubation	Immediately before ML	ML	5 min after extubation
I	Placebo tablets and saline	106 $\pm$ 10	101 $\pm$ 27	95 $\pm$ 23	167 $\pm$ 37	126 $\pm$ 32 **	159 $\pm$ 38 **	114 $\pm$ 29
II	Placebo and fentanyl	107 $\pm$ 10	106 $\pm$ 16	90 $\pm$ 15 *	172 $\pm$ 17 **	78 $\pm$ 16 **	105 $\pm$ 31	127 $\pm$ 11 *
				(groups I + II v. III + IV)		(group I v. III)		(group II v. IV)
III	Metoprolol and saline	104 $\pm$ 14	91 $\pm$ 19	76 $\pm$ 19	142 $\pm$ 25	89 $\pm$ 26 *	138 $\pm$ 27 **	104 $\pm$ 21
IV	Metoprolol, fentanyl and naloxone	105 $\pm$ 12	89 $\pm$ 14	76 $\pm$ 12	138 $\pm$ 31	65 $\pm$ 20	84 $\pm$ 27	104 $\pm$ 12
			↑ Metoprolol 0.2 g, or placebo for 4 days		↑ Fentanyl 1.0 mg, or saline		↑ Naloxone 0.8 mg, or saline	

Fentanyl markedly decreased MAP during undisturbed anaesthesia (third column, table II). The effect of fentanyl on MAP during microlaryngoscopy was pronounced. The effect of fentanyl was abolished after naloxone had been given and the trachea extubated.

Systolic arterial pressure (SAP). Mean values in the four groups were similar in the resting patient before metoprolol or placebo (table III). Before anaesthesia, mean SAP was 22 mm Hg less among subjects receiving metoprolol, than among the others (n.s.). The corresponding figure for the difference in mean values during induction was exactly the same (22 mm Hg, n.s.). The mean SAP at intubation

was 33 mm Hg less among patients given metoprolol, than among the others ($P < 0.01$).

Metoprolol decreased SAP measured immediately before microlaryngoscopy, in the undisturbed patient. The difference in SAP during microlaryngoscopy, between patients receiving metoprolol but no fentanyl (group III), and the controls (group I) was 32 mm Hg (n.s.).

Fentanyl markedly decreased SAP both during undisturbed anaesthesia and during microlaryngoscopy. There was no significant difference between groups after endotracheal extubation.

Heart rate. Mean values of the four groups were similar before metoprolol or placebo (table IV).

TABLE III. Systolic arterial pressure (mm Hg) (group means $\pm$ 1SD). For explanation, see table II

Group		Rest, untreated	5 min before anaesth.	Min. at induction	Max. at intubation	Immediately before ML	ML	5 min after extubation
I	Placebo tablets and saline	149 $\pm$ 18	147 $\pm$ 32	124 $\pm$ 29	225 $\pm$ 65	169 $\pm$ 46 **	214 $\pm$ 51 **	156 $\pm$ 45
II	Placebo, fentanyl and naloxone	147 $\pm$ 17	149 $\pm$ 27	119 $\pm$ 26	219 $\pm$ 27 **	100 $\pm$ 18 *	137 $\pm$ 40	167 $\pm$ 21
					(groups I + II v. III + IV)	(group I v. III)		
III	Metoprolol and saline	142 $\pm$ 24	130 $\pm$ 29	101 $\pm$ 29	184 $\pm$ 33	120 $\pm$ 36 **	182 $\pm$ 31 **	144 $\pm$ 33
IV	Metoprolol, fentanyl and naloxone	141 $\pm$ 20	124 $\pm$ 22	98 $\pm$ 18	177 $\pm$ 39	86 $\pm$ 26	107 $\pm$ 33	142 $\pm$ 17
			↑ Metoprolol 0.2 g, or placebo for 4 days		↑ Fentanyl 1.0 mg, or saline		↑ Naloxone 0.8 mg, or saline	

TABLE IV. Heart rate (beat min⁻¹) (mean ± 1SD). For explanation see table II

Group	Rest, untreated	5 min before anaesth.	Induction	Intubation	Immediately before ML	During ML	5 min after extubation
I Placebo tablets and saline	79 ± 7	63 ± 17	94 ± 16	106 ± 13	90 ± 13	93 ± 12	89 ± 10
II Placebo, fentanyl and naloxone	73 ± 13	65 ± 12	93 ± 12	108 ± 13	80 ± 8	83 ± 9	91 ± 13
		**	**	**	** (I v. III) * (II v. IV)	** (I v. III) ** (II v. IV)	* (I v. III) ** (II v. IV)
III Metoprolol and saline	76 ± 5	49 ± 7	72 ± 9	74 ± 9	68 ± 10	67 ± 11	74 ± 12
IV Metoprolol, fentanyl and naloxone	76 ± 12	50 ± 7	77 ± 11	82 ± 10	68 ± 10	69 ± 10	71 ± 11
	↑ Metoprolol 0.2 g for 4 days, or placebo	↑ Atropine 1.0 mg to all		↑ Fentanyl 1.0 mg, or saline		↑ Naloxone 0.8 mg, or saline	

Metoprolol decreased heart rate significantly before, during and after anaesthesia. The heart rates of patients given fentanyl and naloxone were not significantly different from values obtained from patients given saline instead.

Plasma adrenaline concentrations. Mean values were above the normal range in resting relaxed subjects (see Methods). Mean values decreased during anaesthesia, significantly so in most groups (table V), and increased again during microlaryngoscopy. The increase was less pronounced in patients given fentanyl (groups II and IV) than in the others. There was a significant increase in adrenaline concentration in group IV after naloxone had been given and the trachea extubated. There were no significant differences between patients given metoprolol, and those given placebo.

Plasma noradrenaline concentrations. Mean values

were slightly greater than the normal range for resting relaxed subjects (see Methods). There was an initial slight decrease during anaesthesia in group IV (table VI). Mean values increased in all groups during microlaryngoscopy, with significantly greater values in patients receiving metoprolol but not fentanyl (group III) than in any of the other three groups ($P < 0.05$ or 0.01 ; table V). Mean values decreased after extubation, but significantly so only in group III.

Plasma ACTH concentrations (table VII). Mean values increased greatly during microlaryngoscopy among patients given saline instead of fentanyl (groups I and III), and tended to decrease afterwards. Concentrations during microlaryngoscopy, among patients given fentanyl, were several times lower than in the other groups. There was a significant increase in group IV ($P < 0.01$) after naloxone

TABLE V. Plasma adrenaline concentrations (nmol litre⁻¹) (mean ± 1SD). Significant changes between successive stages, within each group, and differences, between groups, at a certain stage are indicated. * $P < 0.05$, ** $P < 0.01$. As an example, mean concentrations in group II decreased from 0.41 to 0.12 between the first and second blood samples ($P < 0.01$). There was a significant difference in concentration between groups III and IV immediately before and during ML ($P < 0.05$). Otherwise, there were no significant differences between groups

Group	5-15 min before anaesthesia	Immediately before ML	During ML	2 min after extubation
I Placebo and saline	0.57 ± 0.53	0.31 ± 0.27	* 0.91 ± 1.2 ^c	0.59 ± 0.32
II Placebo, fentanyl and naloxone	0.41 ± 0.29	** 0.12 ± 0.05	0.38 ± 0.51	0.43 ± 0.25
III Metoprolol and saline	0.83 ± 0.48	** 0.25 ± 0.13	** 0.84 ± 0.61	0.59 ± 0.42
IV Metoprolol, fentanyl and naloxone	0.67 ± 0.45	** 0.14 ± 0.12	** 0.32 ± 0.24	** 1.01 ± 0.78

TABLE VI. Plasma noradrenaline concentrations, nmol litre⁻¹ (mean $\pm$ 1SD). See table V for explanation

Group	5-15 min before anaesthesia	Immediately before ML		During ML	2 min after extubation
I Placebo and saline	2.0 $\pm$ 0.9	2.3 $\pm$ 0.8	*	4.0 $\pm$ 1.8	3.2 $\pm$ 1.8
II Placebo, fentanyl and naloxone	2.0 $\pm$ 0.7	2.2 $\pm$ 0.9	**	3.5 $\pm$ 1.8	3.2 $\pm$ 1.2
			* (group I v. III)		
III Metoprolol and saline	2.4 $\pm$ 1.2	2.9 $\pm$ 1.4	**	7.4 $\pm$ 3.3 **	** 4.2 $\pm$ 2.5
IV Metoprolol, fentanyl and naloxone	2.5 $\pm$ 1.2	2.1 $\pm$ 1.0	**	3.1 $\pm$ 2.1	2.7 $\pm$ 1.3

TABLE VII. Plasma ACTH concentrations (ng litre⁻¹) (mean $\pm$ 1SD). See table V for explanation

Group	5-15 min before anaesthesia	Immediately before ML		During ML	2 min after extubation
I Placebo tablets and saline	49 $\pm$ 107	48 $\pm$ 66	*	217 $\pm$ 167 *	185 $\pm$ 180
II Placebo, fentanyl and naloxone	13 $\pm$ 24	31 $\pm$ 54	*	24 $\pm$ 27	58 $\pm$ 83
III Metoprolol and saline	33 $\pm$ 38	41 $\pm$ 45	**	174 $\pm$ 114 **	** 113 $\pm$ 97
IV Metoprolol, fentanyl and naloxone	14 $\pm$ 41	18 $\pm$ 40		23 $\pm$ 46	** 74 $\pm$ 81

and extubation of the trachea.

Plasma cortisol concentrations (table VIII). Mean values increased significantly during microlaryngoscopy, in the patients given saline instead of fentanyl (groups I and III). The increase was still evident after anaesthesia in group III. Concentrations during microlaryngoscopy were smaller in the patients given fentanyl. Also, plasma concentrations at this stage were lower in group III (metoprolol) than in group I (control) — a reverse relationship compared with the plasma noradrenaline concentrations.

Plasma metoprolol concentrations. Measurements in groups I and II showed that no patient received metoprolol by mistake. Mean values in groups III and IV were similar during all stages, so the results were pooled. The concentrations were 472 $\pm$ 312 (mean $\pm$ 1SD; range 76-1100) nmol litre⁻¹ before anaesthesia and 541 $\pm$ 300, 551 $\pm$ 331 and 574 $\pm$ 349 nmol litre⁻¹ in the three later samples, the smallest recorded value being 150 nmol litre⁻¹. As mentioned earlier, metoprolol 10 mg was given i.v. after the first sample. The second sample was taken some 10-15 min later.

DISCUSSION

The mean values and inter-individual variation for plasma metoprolol concentrations, obtained by us, agree with the findings of Johnsson and colleagues (1980) on the pharmacokinetics of metoprolol when administered in a slow-release form. Metoprolol 10 mg i.v. increased the plasma concentration only slightly. Rollason and Russell (1980), gave 0.06-0.17 mg kg⁻¹ i.v. and Coleman and Jordan (1980) only 2-4 mg i.v. Presumably, these doses resulted in lower plasma concentrations. Nevertheless, these authors also found that metoprolol was effective in limiting tachycardia during anaesthesia.

Our results in regard to arterial pressure before anaesthesia are consistent with those of Haglund and Collste (1980) who found that metoprolol had decreased systolic/diastolic arterial pressures by 13/11 mm Hg by the 2nd day of treatment, with no further decrease in pressures during the next few months. Nevertheless, the finding by Trimarco and associates (1982), that peripheral vascular resistance continued to decrease for the first 2 years during the

TABLE VIII. Plasma cortisol concentrations, nmol litre⁻¹ (mean ± 1SD). See table V for explanation

Group		5–15 min before anaesthesia	Immediately before ML	During ML	2 min after extubation
I	Placebo tablets and saline	246 ± 154	358 ± 231	** 702 ± 269	747 ± 279
II	Placebo, fentanyl and naloxone	148 ± 71	248 ± 158	284 ± 242	324 ± 227
* (group I v. III)					
III	Metoprolol and saline	166 ± 51	227 ± 138	** 453 ± 190	* 744 ± 336
IV	Metoprolol, fentanyl and naloxone	148 ± 60	155 ± 72	220 ± 150	** 223 ± 155

treatment of hypertension with metoprolol, implies that the changes in arterial pressure during anaesthesia and microlaryngoscopy might have been different, had we pretreated the patients for longer.

Although the pretreatment with metoprolol decreased arterial pressure during intubation and during, and after, anaesthesia and microlaryngoscopy, the fluctuations in mean values of arterial pressure, during anaesthesia, were not greatly affected (fig. 1). In the latter respect, the present findings agree with those obtained after the injection i.v. of the β₁-selective adrenoceptor blocker practolol (Siedlecki, 1975; Werner et al., 1980). Similarly, Pontén and colleagues (1980) found that variations in arterial pressure, during anaesthesia and surgery, were not decreased by continuing, instead of withdrawing, β-blocking therapy.

In contrast, Prys-Roberts and colleagues (1973), studying hypertensive patients under halothane-nitrous oxide anaesthesia, found that both decreases and increases in arterial pressure were attenuated by practolol, whether acutely after injection i.v. or after 2 days of oral pretreatment. However, interpretation of that study is difficult because other antihypertensive drugs were given besides practolol and control patients were obtained retrospectively.

Arterial pressure increased markedly during intubation of the trachea and the increases observed were somewhat greater than those noted by Stoeltzing (1977). Possibly, this was because our patients were somewhat older and, in addition, the arterial pressures before anaesthesia were slightly greater. During the microlaryngoscopy arterial pressures were high in the patients anaesthetized with thiopentone and nitrous oxide only. Although metoprolol did decrease arterial pressure during the various phases of anaesthesia, fentanyl was more

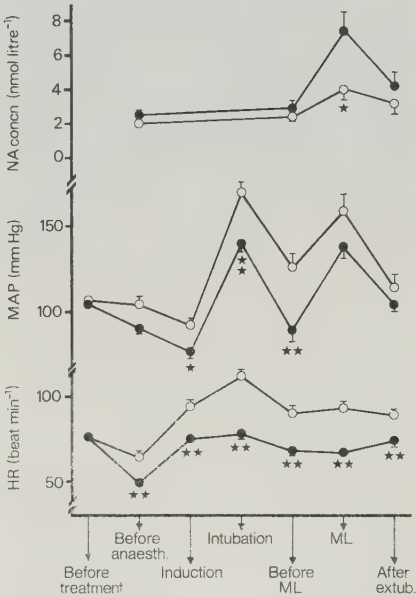


FIG. 1. Comparison of plasma noradrenaline (NA) concentrations, mean arterial pressures (MAP) and heart rates among patients receiving metoprolol (●) or placebo (○). Group mean and 1 SEM. (○) represents pooled values for groups I and II during the first four stages, during which both groups were treated alike. Mean values of groups I and II were, in fact, similar on these occasions as is shown in tables II, III and V, which give a more detailed account of these results. Group II received fentanyl after intubation. Therefore, (○) represents only group I during the last three stages. Similarly, (●) represents groups III and IV during the first four stages, and group III only in the last three. Significant differences between patients given metoprolol, and those given placebo: **P* < 0.05; and ***P* < 0.01.

effective. Therefore, we usually prefer to give fentanyl 0.5–0.8 mg for microlaryngoscopy, fentanyl 0.2–0.4 mg being given before the thiopentone to counteract any hypertension during intubation (Dahlgren and Messeter, 1981). The effect of fentanyl is antagonized by naloxone after microlaryngoscopy. This does not provoke nausea or a circulatory "overshoot reaction" (Magnusson et al., 1982).

Although 20–35% of noradrenaline injected i.v. is removed in a single passage through the lungs (Fishman and Pietra, 1974), we preferred arterial sampling, to sampling from an arm vein, to avoid local factors which could have affected catecholamine concentrations. In view of the very marked arterial pressure response to microlaryngoscopy, in the patients not given fentanyl, it was only to be expected that plasma catecholamine concentrations would be high at this stage. What was remarkable was that the mean plasma noradrenaline concentrations, among patients given metoprolol but not fentanyl (group III), were almost twice those of the control patients (group I). Our findings in this respect are similar to those of Hansson and colleagues (1977). They found that increases in plasma noradrenaline concentration, in response to dynamic exercise, were greater during metoprolol medication than with placebo treatment. One possible explanation for these results is suggested by Esler and associates (1981), who reported that the removal of noradrenaline from plasma was slowed by β -blockade. Therefore, the difference in noradrenaline concentrations, between groups I and III, does not necessarily reflect a difference in overall sympathetic activity. Whatever the reasons for our findings, it is noteworthy that the plasma concentrations of noradrenaline during microlaryngoscopy were high and that direct circulatory effects can be expected (Hjemdahl et al., 1980). Measurements of peripheral vascular resistance in the different groups would have been of great interest in this context.

The pattern of ACTH concentrations was different from that of the catecholamines. The low mean ACTH concentrations, among patients given fentanyl, and the increase after naloxone may be explained by a direct inhibition of ACTH release by opiates (Volavka et al., 1979).

The cortisol concentrations are consistent with the ACTH concentrations, considering the fact that the cortisol response is more sluggish (Krieger, 1979). While cortisol concentrations during micro-

laryngoscopy were significantly greater in group I (placebo tablets, no fentanyl), than in group III (metoprolol, but no fentanyl), the reverse was true regarding noradrenaline. We cannot fully explain the discrepancy, but it certainly illustrates that changes in plasma concentrations of so called "stress hormones" must be interpreted with caution.

Our conclusion from the present study, and a previous one (Werner et al., 1980), is that it is preferable to use opiate analgesia to limit the stress response to microlaryngoscopy. We now seldom use β -blockade in patients not previously receiving such treatment.

ACKNOWLEDGEMENTS

Financial support was received from the Åke Wiberg foundation, Stockholm, and the Medical Faculty, University of Lund. Thanks are due to several members of the scientific staff at Hässle/Astra AB, Gothenburg, for valuable support and criticism. Mrs Britt-Marie Eriksson at the laboratory of Hässle/Astra deserves appreciation for performing the adrenaline and noradrenaline assays. Mrs Gunvor Ekdahl and Anders Beckman, R.N., provided excellent technical assistance.

REFERENCES

- Coleman, A. J., and Jordan, C. (1980). Cardiovascular responses to anaesthesia. Influence of beta-adrenoreceptor blockade with metoprolol. *Anaesthesia*, **35**, 972.
- Conway, J., and Amery, A. (1975). The antihypertensive effect of propranolol and other β -adrenoreceptor antagonists; in *Central Action of Drugs in the Regulation of Blood Pressure* (eds D. Davies and J. Reid), p. 277. London: Pitman Medical Publishing Co. Ltd.
- Dahlgren, N., and Messeter, K. (1981). Treatment of stress response to laryngoscopy and intubation with fentanyl. *Anaesthesia*, **36**, 1022.
- Eriksson, B. M. (1981). Aluminium foil instead of glass plates for thin-layer chromatography in radioenzymic assay. *Clin. Chem.*, **27**, 341.
- Ervik, M. (1975). Quantitative determination of metoprolol in plasma and urine by gas chromatography. *Acta pharmacol. Toxicol. (Cph)*, **36** (Suppl. V), 136.
- Esler, M., Jackman, G., Leonard, P., Skevs, H., Bobik, A., and Jennings, G. (1981). Effect of propranolol on noradrenaline kinetics in patients with essential hypertension. *Br. J. Clin. Pharmacol.*, **12**, 375.
- Fishman, A., and Pietra, G. (1974). Handling of bioactive materials by the lung (second of two parts). *N. Engl. J. Med.*, **291**, 953.
- Haglund, K., and Collste, C. (1980). Time course of blood pressure, pulse rate, plasma renin and metoprolol during treatment of hypertensive patients. *Eur. J. Clin. Pharmacol.*, **17**, 321.

- Hansson, B.-G., Dymling, J.-F., Manhem, P., and Hökfelt, B. (1977). Long term treatment of moderate hypertension with the beta-receptor blocking agent metoprolol. *Eur. J. Clin. Pharmacol.*, 11, 247.
- Hedner, P., Nördén, N. E., and Valdermarsson, S. (1981). Falsely high values for corticotropin by the CIS-Sorin RIA method. *Clin. Chem.*, 27, 1146.
- Hjemdahl, P., Pollare, T., Gillberg, M., and Åkerstedt, T. (1980). Concentration-effect relationships for infused catecholamines in man: Influence of propranolol and metoprolol. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 313, R60.
- Johnsson, G., Jördö, L., Lundborg, P., Regårdh, C.-G., and Rönn, O. (1980). Plasma levels and pharmacological effects of metoprolol administered as controlled release (Dureles) and ordinary tablets in healthy volunteers. *Int. J. Clin. Pharmacol., Ther. Toxicol.*, 18, 292.
- Krieger, D. (1979). Plasma ACTH and corticosteroids; in *Endocrinology (volume 2)* (eds L. DeGroot, G. Cahill, L. Martini, D. Nelson, W. Odell, J. Potts and E. Steinberger), p. 1139. New York: Grune & Stratton.
- Magnusson, J., Werner, O., Carlsson, C., and Pettersson, K. I. (1982). Narcotic antagonism by naloxone. Few side effects after a short procedure. *Anaesthesia*, (in press).
- Peuler, J., and Johnson, G. (1977). Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. *Life Sci.*, 21, 625.
- Pontén, J., Biber, B., Henriksson, B. Å., Hjalmarsson, Å., and Lundberg, D. (1980). β -receptor blockers and neuroleptanaesthesia; in *β -Blockade and Anaesthesia* (eds P. Poppers, B. van Dijk and A. van Elzacker), p. 172. Rijswijk, the Netherlands: Astra Pharmaceutika BV.
- Prys-Roberts, C., Föex, P., Biro, G. P., and Roberts, J. G. (1973). Studies of anaesthesia in relation to hypertension. V: Adrenergic beta-receptor blockade. *Br. J. Anaesth.*, 45, 671.
- Rollason, W. N., and Russell, J. G. (1980). Intravenous metoprolol and cardiac dysrhythmias. An evaluation in the management of dysrhythmias in outpatient dental anaesthesia. *Anaesthesia*, 35, 783.
- Siedlecki, J. (1975). Disturbances in the function of cardiovascular system in patients following endotracheal intubation and attempts of their prevention by pharmacological blockade of sympathetic system. *Anesth. Resusc. Intens. Ther.*, 3, 107.
- Stoelting, R. K. (1977). Circulatory changes during direct laryngoscopy and tracheal intubation. Influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology*, 47, 381.
- Trimarco, B., Wikstrand, J., Buzzetti, G., Ricciardelli, B., DeLuca, N., Volpe, M., and Condorelli, M. (1982). Regression of left ventricular hypertrophy and improvement of left ventricular function after long-term antihypertensive treatment with metoprolol. *Abstract, 9th Scientific Meeting of the International Society of Hypertension, Mexico City*.
- Weigand, H. (1970). Über die Narkose bei der Mikrolaryngoskopie und endolaryngealen Mikrochirurgie. II. Das reflektorische Kreislaufverhalten und seine Beeinflussung durch Oberflächenanästhetika. *Anaesthetist*, 19, 131.
- Werner, O., Magnusson, J., Fletcher, R., Nilsson-Ehle, P., and Pahlm, O. (1980). I.v. praxetol during microlaryngoscopy. Effect on arterial pressure, heart rate, blood glucose and lipolysis. *Br. J. Anaesth.*, 52, 91.
- Volavka, J., Cho, D., Malliya, A., and Bauman, J. (1979). Naloxone increases ACTH and cortisol levels in man. *N. Engl. J. Med.*, 300, 1056.

REPONSES DU METOPROLOL, DU FENTANYL ET DU "STRESS" A LA MICROLARYNGOSCOPIE

Effets sur la tension artérielle, le rythme cardiaque et les concentrations de catécholamines, d'ACTH et de cortisol

RESUME

Quarante patients soumis à une microlaryngoscopie ont été anesthésiés au moyen de thiopentone et d'oxyde nitreux. Vingt d'entre eux ont pris 200 mg de metoprolol sous forme de comprimé retard une fois par jour pendant 4 jours jusqu'au matin de l'opération inclus, ainsi que 10 mg i.v. peu de temps avant l'induction de l'anesthésie. Aux autres patients, il a été administré des comprimés de placebo ainsi que des solutions physiologiques salines i.v. On a ensuite divisé par moitié ces deux groupes auxquels on a administré en cours d'anesthésie 1,0-1,5 mg de fentanyl dont l'effet a été antagonisé par de la naloxone en fin d'anesthésie. Les autres patients ont reçu une solution saline i.v. au lieu et place du fentanyl ou de la naloxone. Le metoprolol a eu pour effet de faire baisser le rythme cardiaque et le niveau général de la tension artérielle pendant l'anesthésie, bien qu'il n'ait pas affecté les fluctuations de tension. Comparé au placebo, le metoprolol a eu pour effet d'accroître les concentrations dans le plasma de noradrénaline artérielle et inversement de faire baisser les concentrations de cortisol. Le fentanyl a fait descendre la tension artérielle et les concentrations d'ACTH et de cortisol dans le plasma, que le patient ait reçu ou non du metoprolol. Les concentrations de noradrénaline et d'adrénaline dans le plasma ont diminué sous l'effet du fentanyl chez les patients auxquels on avait administré du metoprolol.

METOPROLOL, FENTANYL UND STRESSREAKTIONEN AUF MIKROLARYNGOSKOPIE

Wirkung auf Blutdruck, Herzfrequenz und Plasmaspiegel von Katecholaminen, ACTH und Cortisol

ZUSAMMENFASSUNG

Vierzig Patienten wurden zur Mikrolaryngoskopie mit Thiopenton und Lachgas anästhetisiert. Zwanzig Patienten erhielten 200 mg Metoprolol in einer retard-Tablette vier präoperative Tage einmal täglich und am Morgen vor der Operation, außerdem 10 mg i.v. kurz vor der Narkoseeinleitung. Die anderen Patienten erhielten Placebo-Tabletten und physiologisches Kochsalz i.v. Beide Gruppen von je zwanzig Patienten wurden weiter unterteilt, wobei jeweils die Hälfte von ihnen während der Narkose 1,0-1,5 mg Fentanyl erhielt, dessen Wirkung bei Narkoseende durch Naloxon antagonisiert wurde. Die andere Hälfte erhielt Kochsalz i.v. anstelle von Fentanyl oder Naloxon. Metoprolol reduzierte während der Narkose die Herzfrequenz und die allgemeine Höhe des Blutdrucks, beeinflusste jedoch nicht die blutdruckschwankungen. Der arterielle Noradrenalin-Spiegel während der Mikrolaryngoskopie wurde durch Metoprolol verglichen mit dem Placebo erhöht, der Cortisol-Spiegel dagegen erniedrigt. Fentanyl verringerte den Plasma-ACTH-Spiegel, den Cortisol-Spiegel und den arteriellen Blutdruck, wobei vorübergehende Metoprololgabe keine Rolle spielte. Bei Patienten mit Metoprolol führte Fentanyl zu einer niedrigeren Plasma-Adrenalin- und Noradrenalin-Konzentration.

RESPUESTAS DEL METOPROLOL,
DEL FENTANILLO Y DE DEPRESIÓN A LA
MICROLARINGOSCOPIA

Efectos sobre la presión arterial, el ritmo cardíaco y las concentraciones de catecolaminas, de ACTH y de cortisol

SUMARIO

Se administró una anestesia con tiopentona y óxido nítrico a cuarenta pacientes sometidos a microlaringoscopia. Se administró 200 mg de metoprolol a veinte pacientes en forma de pastilla a efecto remanente una vez al día durante 4 días hasta la mañana incluida de la operación y 10 mg i.v. poco antes la inducción de la anestesia. A los otros pacientes, se les administró pastillas de placebo y solución salina fisiológica i.v. Ambos grupos de 20

pacientes fueron subdivididos una vez más, la mitad de los pacientes recibiendo 1,0–1,5 mg de fentanilo durante la anestesia, cuyo efecto fue antagonizado con naxolona al fin de la operación. Los demás pacientes recibieron solución salina i.v. en vez del fentanilo o de la naxolona. El metoprolol hizo bajar el ritmo cardíaco y el nivel general de la presión arterial durante la anestesia, pero no afectó las fluctuaciones en la presión. Las concentraciones de noradrenalina en el plasma arterial durante la microlaringoscopia fueron realizadas por el metoprolol, en comparación con el placebo, pero ocurrió el contrario para las concentraciones de cortisol. El fentanilo hizo bajar la presión arterial, el ACTH del plasma y las concentraciones de cortisol, independientemente del hecho que el paciente había recibido o no metoprolol. Las concentraciones de noradrenalina y de adrenalina en el plasma bajaron bajo el efecto del fentanilo en los pacientes que habían recibido metoprolol.

Narcotic antagonism by naloxone

Few side-effects after a short procedure?

J. MAGNUSSON, O. WERNER, C. CARLSSON AND K. I. PETTERSSON

Summary

Twenty patients undergoing microlaryngoscopy were anaesthetised with thiopentone and nitrous oxide. Half of the patients received 1.0–1.5 mg of fentanyl during anaesthesia, the effect of which was antagonised by naloxone 0.4 mg intravenously and 0.4 mg subcutaneously. The other patients served as controls and received saline instead of fentanyl and naloxone. Fentanyl markedly reduced mean arterial pressure and the heart rate-systolic arterial pressure product during microlaryngoscopy. Conversely, there were significant increases in these measurements after naloxone had been given. However, there were no significant differences between patients given fentanyl with naloxone, and those given saline, in respect of arterial pressure, heart rate or dysrhythmia during recovery. No patient vomited, or appeared nauseated when observed afterwards in the operating room. One patient vomited several hours after naloxone.

Key words

Analgesics; narcotic.

Antagonists; narcotic.

Blood pressure; drug effects.

Hypertension,¹ dysrhythmia,^{2,3} pulmonary oedema⁴ and vomiting⁵ have been noticed when naloxone has been used to antagonise the effects of narcotics. Therefore, it is often prudent to limit the amount of opiate analgesics given during general anaesthesia, in order to reduce the need for opiate antagonism afterwards. However, such a policy may come in conflict with the need for adequate analgesia, particularly during short procedures.

Serious side-effects to naloxone have usually been reported after major operations, lasting at least a couple of hours,^{1–5} so the response may be different after very short procedures, especially those that do not leave a painful wound.

Over the last few years, the practice at our hospital has shifted towards an increasing use of opiates during general anaesthesia for one short procedure, namely microlaryngoscopy. Naloxone has been used afterwards, in most patients. We have seldom observed any side-effects, even after relatively large doses of naloxone. In order to study this in greater depth, a randomised comparison was carried out between our previous anaesthetic technique for microlaryngoscopy, which involved the use of thiopentone, nitrous oxide and suxamethonium, and a technique whereby generous doses of fentanyl were added during anaesthesia, and naloxone supplied afterwards. Arterial pressure,

J. Magnusson, MD, O. Werner, MD, C. Carlsson, Assistant Professor, Department of Anaesthesia, K.I. Pettersson, MD, Department of ENT Surgery, University Hospital, S-221 85 Lund, Sweden.

0003-2409/83/020103 + 05 \$03.00/0 © 1983 The Association of Anaesthetists of Gt Britain and Ireland

heart rate and dysrhythmia during recovery were studied. The rate-pressure product, or double product,⁶ was computed as a rough index of myocardial oxygen consumption. The presence of nausea and vomiting was noted.

Patients and methods

Twenty patients undergoing microlaryngoscopy were studied. They were not under treatment with antihypertensive or anti-dysrhythmic drugs such as β -blockers or digitalis. All patients were seen at a pre-operative visit, at which time informed consent was obtained and arterial pressure measured with a mercury manometer. They were then divided in two groups, with 10 in each, by stratified randomisation according to the level of systolic arterial pressure: *group 1*, patients given only thiopentone and nitrous oxide as anaesthetic drugs; *group 2*, patients given thiopentone and nitrous oxide, as group 1, in addition, they received i.v. fentanyl shortly before microlaryngoscopy, and naloxone afterwards.

Assignment to the different groups was double-blind. Thus, patients not given fentanyl and naloxone received equivalent volumes of saline. Often, however, it was obvious to which group the patient belonged, because of the response during anaesthesia. Information about what drugs were given was immediately available, should the need have arisen.

Patients were premedicated with morphine and hyoscine i.m. according to age (Table 1). A plastic radial artery cannula was placed 10–30 minutes before anaesthesia and arterial pressure was measured with an HP 1280 C transducer (Hewlett Packard) and continuously written on a Mingo-graph 80 (Siemens Elema) together with an ECG lead (modified V₅). Calibration of the transducer against a water column corresponding to 100 mmHg was performed each day. Day-to-day variation was small, so calibration over the full range (0–300 mmHg) was only performed once. Correction was applied for a slight alinearity of the pressure-recording system.

One mg of atropine was given 4 minutes before anaesthesia. Anaesthesia was induced with thiopentone and tracheal intubation with a Portex 6.5 tracheal tube was facilitated with suxamethonium (Table 1). Subsequently, the lungs were ventilated manually with 70% nitrous oxide in oxygen. Fentanyl 1.0 mg or saline, was given in divided i.v. doses 0–8 minutes before micro-

Table 1. Some comparisons of patients given/not given fentanyl with naloxone. Values are mean (SD) (when applicable)

	Control	Fentanyl + naloxone
Males/females	9/1	8/2
Age (years)	65 (11)	61 (13)
Weight (kg)	80 (21)	71 (12)
Premedication		
Morphine (mg)	6.5 (3.2)	6.3 (2.9)
Hyoscine (mg)	0.26 (0.12)	0.25 (0.12)
Thiopentone (mg/kg)	4.3 (0.7)	4.4 (0.8)
Suxamethonium (mg/kg)		
Induction	1.0 (0.2)	1.0 (0.1)
Maintenance	5.3 (3.1)	2.9 (2.1)
Time intervals (min)		
Premedication-anaesthesia	106 (65)	96 (24)
Start-end of ML	8 (2)	11 (8)
End of ML-extubation	8 (2)	7 (2)

ML = microlaryngoscopy.

laryngoscopy with the Kleinsasser instrument. An additional dose of 0.5 mg fentanyl, or saline, was given after 20 minutes, if microlaryngoscopy lasted that long. A suxamethonium infusion ensured adequate muscle relaxation during operation. Naloxone hydrochloride 0.4 mg i.v. + 0.4 mg s.c., or saline, was given 3 minutes after microlaryngoscopy. At least 2 minutes were allowed to elapse with unchanged manual ventilation. Ventilation was then reduced and 100% oxygen was administered as soon as adequate spontaneous ventilation was established, as judged by the anaesthetist's appraisal of respiratory depth and rate. The trachea was extubated soon thereafter.

Calculations

Mean arterial pressure (MAP) at rest 3 days before microlaryngoscopy was calculated as: systolic pressure $\times$ 1/3 + diastolic pressure $\times$ 2/3. MAP on all other occasions was obtained from the arterial pressure tracing. Heart rate and dysrhythmia were evaluated from the ECG. The observer did not know to which group the patient belonged.

Statistics

The Wilcoxon (two-sided) rank sum test for paired data was used for assessing the significance of changes within groups. The Mann-Whitney

(two-sided) rank sum test for unpaired data was used for between-group comparisons. Probability values below 0.05 were considered to indicate statistical significance. The second level of significance used was 0.01. Changes in relation to resting values in the untreated patient were compared, rather than the directly recorded values. Differences, between the groups, in respect of the incidence of dysrhythmia were assessed by Fisher's exact test.

Results

There were no notable differences between patients given fentanyl with naloxone and those given i.v. saline instead, in respect of sex, age, weight, drugs given or duration of the procedure, except that patients given fentanyl required less suxamethonium (Table 1).

One patient in group 1 (controls) was re-intubated because of severe laryngospasm. Post-anaesthetic measurements of arterial pressure and heart rate were not considered representative in this patient and were discarded. We observed the patients in the operating room for about 15 minutes following extubation. No patient vomited or appeared nauseated during this period. However, one control patient (group 1) complained of nausea both before anaesthesia and after anaesthesia, in the ward. One patient given naloxone (group 2) who had gall bladder disease vomited 4–5 hours after anaesthesia shortly after resuming oral intake of fluids. No patients needed extra naloxone. All patients were discharged the next day.

Heart rate

This tended to be somewhat faster among the controls, but on no occasion was this significant (Fig. 1).

Mean arterial pressure (MAP)

This was similar in the two groups before anaesthesia (Fig. 1). Mean MAP during microlaryngoscopy was 159 mmHg among the controls and 54 mmHg less among patients given fentanyl ($p < 0.01$). A significant difference in MAP, of 35 mmHg, remained after microlaryngoscopy, immediately before naloxone or saline ($p < 0.01$). Mean MAP increased by 20 mmHg during the first 2 minutes after naloxone in group 2 ($p <$

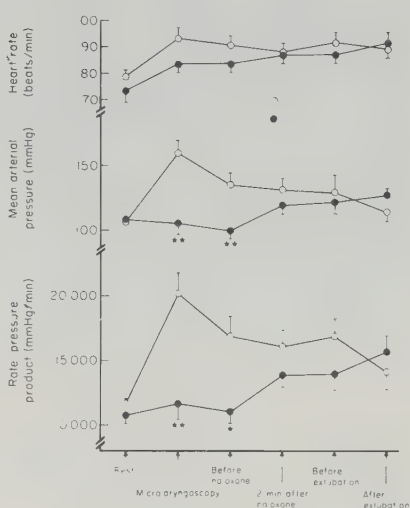


Fig. 1. Cardiovascular changes (mean and 1 SE) during and after microlaryngoscopy. Measurements were taken on the following occasions: at rest during the pre-operative visit; after 10 minutes of microlaryngoscopy or 2 minutes before the end of microlaryngoscopy, whichever came first; immediately before naloxone, i.e. about 3 minutes after microlaryngoscopy; 2 minutes after naloxone; immediately before extubation, i.e. about 5 minutes after naloxone; and finally 5 minutes after extubation. Significant differences between groups on each occasion are indicated: ** $p < 0.01$; * $p < 0.05$. ○ = control; ● = fentanyl + naloxone.

0.01), there being a further increase by 8 mmHg (not significant) up to the point 5 minutes after extubation. During the same period, MAP tended to decrease among the controls. However, there were no significant differences between the groups at any time after naloxone (or corresponding volumes of saline).

Heart rate-systolic arterial pressure product (RPP)

Mean values before anaesthesia were similar in the two groups. There was a large increase among the controls during microlaryngoscopy, which was not seen in group 2 (Fig. 1). A significant difference between the groups remained after microlaryngoscopy and before naloxone. Mean RPP increased significantly after naloxone in group 2 ($p < 0.01$), but there were no significant differences between the groups at any time after naloxone (saline).

Dysrhythmia during recovery

In group 1 (controls), eight patients had extrasystoles that were judged to be supraventricular (SVES). One of these patients also had frequent ventricular extrasystoles (VES), another had three consecutive SVES at extubation. In group 2 (fentanyl + naloxone), occasional SVES were seen in three patients. A few VES were seen in one patient shortly after extubation. The difference between the groups, in respect of the incidence of SVES or VES, was not significant. No instance of serious dysrhythmia was seen, such as A-V block or ventricular tachycardia.

Discussion

In the present study, very high arterial pressures were found during microlaryngoscopy among patients anaesthetised only with thiopentone/nitrous oxide. This agrees with previous findings.⁷⁻⁸ MAP in our patients increased by 20–30 mmHg after naloxone. This is a somewhat greater increase than has been reported by Purdell-Lewis⁹ after 0.4 mg of naloxone. He gave smaller doses of fentanyl during operation, however. Although large increases in MAP were observed in group 2 after naloxone in the present study, arterial pressure and heart rate after microlaryngoscopy were not significantly different among the controls. Moreover, fentanyl offered effective protection against the more severe hypertension during microlaryngoscopy. When total effects are considered, in terms of circulatory stress responses during anaesthesia and recovery, the technique involving fentanyl and naloxone was therefore perhaps preferable to the more superficial anaesthesia given to the control group.

Nausea and vomiting were very common when Longnecker *et al.*⁵ administered naloxone to reverse the effects of i.v. morphine. The morphine was used to supplement general anaesthesia with a mean duration of 2.5 hours. These authors suggested that the vomiting was a withdrawal effect. There are studies in animals which tend to support the notion that opiate dependence may in fact develop within hours. Thus, Martin & Eades¹⁰ elicited marked withdrawal symptoms in dogs by giving nalorphine 8 hours after the start of a morphine infusion. Meyer & Sparber¹¹ gave 0.5 mg/kg of naloxone to rats 2–4 hours after a single dose of morphine. They noticed

behavioural changes suggestive of abstinence. Experimental data in man are more sparse, but Nutt & Jasinsky¹² observed symptoms of abstinence, when naloxone was administered 24 hours after a single 30 mg dose of morphine. One (of six) subjects studied by Evans *et al.*¹³ experienced transient anxiety, sweating, palpitation and hypertension after 1.6 mg of naloxone i.v. Morphine had been given less than 3 hours earlier. Both the vomiting⁵ and the adverse circulatory response¹⁻⁴ reported after narcotic-supplement anaesthesia followed by naloxone can thus, at least partly, be explained as withdrawal phenomena.¹⁴ Our results are in contrast to the findings just cited. We observed no vomiting after naloxone, and had little evidence for a circulatory 'overshoot reaction'.¹⁵ We offer three explanations for the discrepancy, all of which may have contributed. Firstly, hyoscine, which we used for premedication, has anti-emetic properties.¹⁶ Second, the major dose of narcotic (1.0–1.5 mg of fentanyl) was administered less than 30 minutes before naloxone. It is unlikely that such a short exposure induces dependence to narcotic analgesics. Third, postoperative pain was probably minimal among our patients.

The use of generous doses of fentanyl and naloxone for microlaryngoscopy may have certain advantages: the hypertensive response to endoscopy is attenuated; the need for other anaesthetics or muscle relaxants is reduced; according to our experience, the patient is alert with intact protective reflexes shortly after endoscopy. Perhaps, the last point may also be cited as a disadvantage, since, for example, excessive coughing may be uncomfortable for the patient. Cost is a drawback.

Adams & Pybus¹⁷ observed serious respiratory depression more than 4 hours after 0.475 mg of fentanyl to an adult. The effect of i.v. naloxone is too shortlived to prevent this.¹³ This is why we gave half of the naloxone (0.4 mg) s.c. However, we cannot guarantee that this is a safe dose since naloxone kinetics after s.c. injection have not been widely studied. Consequently, we use the fentanyl/naloxone technique only when there is adequate surveillance for several hours after anaesthesia. Also, it is our usual practice to give less fentanyl (0.5–0.8 mg) than the doses employed for the present study. The same amount of naloxone is given (0.4 mg i.v. and 0.4 mg s.c.).

Our continued experience is that nausea,

vomiting and shivering are very uncommon when naloxone is used after microlaryngoscopy or bronchoscopy. Serious circulatory side-effects have not occurred. However, the potential risks with the technique should be remembered. Therefore, the technique must be used with care until its advantages and disadvantages have been studied in larger groups of patients.

Acknowledgments

This study was supported by the Medical Faculty of Lund and the Åke Wiberg Foundation, Stockholm. The assistance of Anders Beckmann, RN, is greatly appreciated.

References

1. ESTILO AE, COTTRELL JE. Naloxone, hypertension, and ruptured cerebral aneurysm. *Anesthesiology* 1981; **54**: 352.
2. AZAR I, TURNDORF H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesthesia and Analgesia* 1979; **58**: 524-5.
3. MICHAELIS LL, HICKEY PR, CLARK TA, DIXON WM. Ventricular irritability associated with the use of naloxone hydrochloride. *Annals of Thoracic Surgery* 1974; **18**: 608-14.
4. FLACKE JW, FLACKE WE, WILLIAMS GD. Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. *Anesthesiology* 1977; **47**: 376-8.
5. LONGNECKER DE, GRAZIS PA, EGGERS GWN. Naloxone for antagonism of morphine-induced respiratory depression. *Anesthesia and Analgesia* 1973; **52**: 447-53.
6. SCHEUER J, PENPARGKUL S. Myocardial metabolism. In: Willerson JT, Sanders CA, eds. *Clinical Cardiology*. New York: Grune and Stratton, 1977: 47-63.
7. WEIGAND H. Über die Narkose bei der Mikrolaryngoskopie und endolaryngealen Mikrochirurgie, II. Das reflexorische Kreislaufverhalten und seine Beeinflussung durch Oberflächen-anaesthetica. *Anaesthesist* 1970; **19**: 131-9.
8. WERNER O, MAGNUSSEN J, FLETCHER R, NILSSON-EHLE P, PAHLM O. I.v. practolol during microlaryngoscopy. Effect on arterial pressure, heart rate, blood glucose and lipolysis. *British Journal of Anaesthesia* 1980; **52**: 91-6.
9. PURDELL-LEWIS JG. Studies of fentanyl-supplemented anaesthesia: Effect of naloxone on the circulation and respiration. *Canadian Anaesthetists' Society Journal* 1980; **27**: 323-9.
10. MARTIN WR, EADES CG. Demonstration of tolerance and physical dependence in the dog following a short-term infusion of morphine. *Journal of Pharmacology and Experimental Therapeutics* 1961; **133**: 262-70.
11. MEYER DR, SPARBER SB. Evidence of possible opiate dependence during the behavioural depressant action of a single dose of morphine. *Life Sciences* 1977; **21**: 1087-94.
12. NUTT JG, JASINSKI DR. Methadone-naloxone mixtures for use in methadone maintenance programs. An evaluation in man of their pharmacological feasibility. II. Demonstration of acute physical dependence. *Clinical Pharmacology and Therapeutics* 1974; **15**: 156-66.
13. EVANS JM, HOGG MIJ, LUNN JN, ROSEN M. Degree and duration of reversal by naloxone of effects of morphine in conscious subjects. *British Medical Journal* 1974; **2**: 589-91.
14. MARTIN WR. Naloxone. *Annals of Internal Medicine* 1976; **85**: 765-8.
15. PATSCHKE D, EBERLEIN HJ, HESS W, TARNOW J, ZIMMERMANN G. Antagonism of morphine with naloxone in dogs. Cardiovascular effects with special reference to the coronary circulation. *British Journal of Anaesthesia* 1977; **49**: 525-33.
16. WOOD-SMITH FG, VICKERS MD, STEWART HC. *Drugs in anaesthetic practice*. 4th ed. London: Butterworths, 1973: 330.
17. ADAMS AP, PYBUS DA. Delayed respiratory depression after use of fentanyl during anaesthesia. *British Medical Journal* 1978; **1**: 278-9.

HAEMODYNAMIC EFFECTS OF METOPROLOL PRETREATMENT IN HYPERTENSIVE PATIENTS UNDERGOING SURGERY

J. Magnusson*, T. Thulin**, O. Werner*, J. Järhult*** and D. Thomson*.

Departments of Anaesthesia*, Medicine** and Surgery***,
University Hospital of Lund, S-221 85 LUND, Sweden.

Thirty hypertensive patients scheduled for cholecystectomy or hernia repair under general anaesthesia with thiopentone/fentanyl/nitrous oxide/pancuronium were divided into two groups of fifteen. One group received metoprolol tablets, 200 mg in a slow release form, once daily for at least two weeks including the morning of surgery. In addition, 15 mg of metoprolol was injected i.v. shortly before anaesthesia induction. The other group received placebo tablets and saline. Two patients in the treatment group and one patient in the placebo group were subsequently excluded, because of complications during treatment.

Metoprolol significantly reduced arterial pressure both during undisturbed anaesthesia, during intubation and after extubation. A similar tendency was observed also during surgery, although it was not quite significant ($p = 0.055$). However, metoprolol had no effect on variations in systemic vascular resistance. Mean pulmonary arterial pressure during anaesthesia and surgery was significantly greater among the controls, than in the metoprolol group. Central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP) increased significantly in both groups in response to the surgical stimulus. There was no significant difference between the groups in PAOP and CVP. One patient in the metoprolol group had marked bradycardia (minimum heart rate 26 min^{-1}) after neostigmine and atropine; otherwise metoprolol pretreatment was well tolerated.

The question whether patients with untreated hypertension should receive preoperative hypotensive treatment has not, to our knowledge, been the subject of a randomized clinical trial, although it has been widely discussed. Goldman and Caldera (1979) found no evidence that patients with mild or moderate hypertension benefited from preoperative antihypertensive treatment, while Prys-Roberts and colleagues (1973), who mainly studied patients with more severe hypertension, found that an improved cardiovascular stability during anaesthesia was achieved by the use of beta-blockers. We have studied the haemodynamic effects of preoperative treatment with the cardioselective betablocker metoprolol in a double-blind trial.

METHODS

The study was approved by the local Human Investigations Committee. From the hospital's computer files, a list was obtained of all patients between 30 and 70 years of age, who on January 1, 1981 awaited cholecystectomy or hernia repair. There were 309 such patients. A letter was sent out inviting them for a check-up before surgery. Those who did not respond were contacted by telephone. 294 patients appeared for examination, which included an arterial pressure measurement by a trained nurse after 10 minutes of supine rest. Those with a systolic arterial pressure (SAP) above 170 mm Hg or a diastolic arterial pressure (DAP) above 100 mm Hg, and those already receiving treatment were referred to one of us (TT) for further examination. He made repeated arterial pressure measurements to confirm the presence of hypertension, and obtained a complete medical history. A physical examination was done and chest X-rays and an ECG were taken.

Patients with obstructive lung disease, previous myocardial infarction, congestive heart failure or second and third degree AV-block were not considered for further study. Thirty suitable patients with hypertension were found. They received verbal and written information about the study, after which their consent was obtained. Thirteen of the patients were previously untreated. In the remaining seventeen, antihypertensive therapy (table I) was gradually withdrawn during one week under close medical supervision. They were without therapy for at least two weeks (range 2-3 weeks). Subsequently, the patients were divided into two groups of fifteen by stratified randomization according to whether age was above or below 60 years and whether mean (systolic/3 + diastolic x 2/3) arterial pressure (MAP) was above or below 125 mm Hg. The treatment group received metoprolol tablets, 200 mg, in a slow release form, once daily for at least two weeks (mean 21 days, range 14-34 days) up to and including the morning of surgery. The patients were asked to contact the clinic if symptoms such as malaise, headache, tremor, palpitation or angina pectoris appeared. Those with very high arterial pressure were controlled at intervals of a few days.

Table I. Previous antihypertensive therapy

	Previously untreated						
		β-blocker	β-blocker and diuretic	β-blocker and vasodilator	β-blocker, vasodilator and diuretic	β-blocker, vasodilator, diuretic and α-adrenoceptor agonist	Diuretic
Control group	9	1	3	0	0	0	1
Treatment group	2	2	2	2	1	1	3

On the morning of surgery, morphine and hyoscine according to age was injected i.m. one hour before arrival in the operating room (table II). There, an i.v. cannula was placed and 0.5 mg of atropine was injected i.v. An infusion of glucose, 5.5 % with 80 mmol NaCl liter⁻¹, was started. 500-1000 ml of this was given up to the end of anaesthesia. Under local anaesthesia, a catheter was advanced up the radial artery into the brachial artery. A flow-directed 7 F triple-lumen balloontipped thermodilution pulmonary arterial catheter was inserted via a cubital vein during continuous monitoring of ECG and pressure. Diazepam 2.5-5 mg was given as needed during insertion of the catheters. ECG (modified lead V₅) was recorded continuously on a Mingograph-81 (Siemens-Elema, Stockholm) along with systemic and pulmonary arterial pressure which were measured with HP 1280 C transducers (HewlettPackard). Mean pressures were obtained electronically (Werner & Benthin, 1982). The midaxillary line was used as zero reference level. The pressure transducers were calibrated daily against a mercury manometer.

Anaesthesia was induced with fentanyl, 4 µg kg⁻¹, followed 2 min later by thiopentone (2-3 mg kg⁻¹) until the eye-lash reflex disappeared. After mask ventilation with oxygen, orotracheal intubation was performed with pancuronium (0.1 mg kg⁻¹) as a muscle relaxant. The laryngoscope was held in place to visualize the vocal cords for exactly 30 s. Subsequently, the lungs were ventilated with 70 % N₂O in O₂ with a Servo Ventilator (Siemens-Elema). During the first 10 min of mechanical ventilation, inspired volume was adjusted so that end-tidal PCO₂, as measured with a CO₂ Analyser 930 (SiemensElema), was about 4.5 kPa. Subsequently, ventilation was not changed. Shortly before the start of surgery, fentanyl 2 µg kg⁻¹ was given. Another 1.5 µg kg⁻¹ was administered after 25-30 min of surgery, and thereafter intermittently

every 30-45 min. Patients undergoing cholecystectomy received an intercostal block with 15 ml of 0.5 % bupivacaine at the end of surgery. Subsequently, atropine, 1.0-1.5 mg, and neostigmine, 2.0-3.0 mg were given i.v. The inspired gas mixture was changed to 100 percent oxygen. The patients were extubated when they were awake and had adequate muscular strength. Afterwards, supplementary oxygen was given by mask. Before transfer to the postoperative ward, the arterial and pulmonary arterial catheters were removed. Thereafter, arterial pressure was obtained by sphygmomanometry. Heart rate was obtained from an ECG monitor. On the first postoperative day antihypertensive treatment was (re)instituted in all patients. Usually metoprolol was chosen.

Measurements. Results from the following stages are reported:

0. In the out-patient clinic, on the final visit before starting metoprolol or placebo treatment.
1. 10 min before anaesthesia induction. By this time, the patient had been allowed to settle down for at least 10 min after insertion of the catheters. Metoprolol, 15 mg, or saline had been given i.v. about 15 min previously.
2. During or shortly after intubation when MAP had reached its maximum. This usually occurred about 60 s after inserting the laryngoscope.
3. During undisturbed anaesthesia, shortly before surgical incision.
4. After 20 min of surgery. At this point, the surgeon was usually freeing the cystic duct or the hernia. In two patients, with very high arterial pressure, the measurements were done already after 10 and 15 min, respectively. This was in order not to postpone treatment with sodium nitroprusside, which started immediately afterwards.
5. When MAP was at its maximum during surgery. In about 3/4ths of the patients this occurred within 10 min after occasion 4.

6. About 5 min after extubation. Oxygen supplementation was temporarily discontinued for 3-4 min before taking the blood gas samples.

A complete set of measurements was made on occasions 1, 3, 4 and 6. These included cardiac output, which was obtained in duplicate or triplicate with an IL 701 (Instrumentation Laboratory) thermodilution cardiac output computer. Ten ml of ice-chilled (5 percent) glucose was injected with a pump at the start of expiration via the side-hole of the pulmonary arterial catheter. Injectate temperature was measured with a flow-through probe. The thermodilution curves were written on a recorder (IL 702, Instrumentation Laboratories), so that artifacts could be detected. Systolic and mean arterial pressures were noted together with central venous, mean pulmonary arterial and pulmonary arterial occlusion pressures (CVP, MPAP and PAOP). Cardiac index (CI) was obtained by dividing cardiac output with body surface area (DuBois & DuBois, 1916), and systemic vascular resistance index (SVRI) as: $(MAP-CVP)/CI$. Pulmonary vascular resistance index (PVRI) was obtained as $(MPAP-PAOP)/CI$. Heparinized blood samples from the arterial and pulmonary arterial catheters were taken in two ml plastic syringes and placed in ice + water. They were analyzed for PCO_2 and PO_2 within 10 min on an IL 413 Blood Gas Laboratory (Instrumentation Laboratory). Arterial samples for measurement of plasma metoprolol concentration were taken in heparinized tubes and immediately centrifuged. Plasma was stored at $-70^{\circ}C$ until analyzed as described by Ervik (1975). The ECG recording was scrutinized to identify arrhythmia and downward sloping ST segments. Sinus tachycardia and bradycardia were not classified as arrhythmias.

Statistics. The Mann-Whitney (two-sided) rank sum test for unpaired data was used for between-group comparisons. The significance of changes within groups was analyzed with the Wilcoxon (two-sided) rank sum test for paired data. Probability values less than 0.05 were considered to indicate statistical significance.

RESULTS

One patient, who subsequently proved to belong to the control group and who had a history of angina pectoris, complained of increasing chest pain the last week before the intended surgery. Surgery was postponed and the patient excluded from further study. Similarly, one patient in the treatment group was excluded because dizziness had made her stop taking the tablets. In another treated patient surgery was cancelled because of the appearance of new T-wave inversions on the ECG. In the remaining patients (14 controls, 13 treated) there were no large difference in respect of age, type of surgery, drugs given or the duration of the procedure (table II). However, the controls weighed more than those in the treatment group. Thus, the six patients who weighed 100 kg or more were all allotted to the control group. In order to assess whether this skewness affected the conclusions, the data in the tables and figures are presented with these patients both included and excluded. The text refers to all patients, unless explicitly stated.

There were no surgical complications and no patient needed blood transfusions. One patient in the control group had signs of cardiac failure immediately after extubation with venous congestion, pulmonary rales and a PAOP of 30 mm Hg. At this point systolic arterial pressure was 250 mm Hg.

Table II. Comparison between the groups. Values are given as number of patients, mean $\pm$ 1 SD or median (range). *, ** = significant difference from the treatment group ($p < 0.05$ and 0.01 , resp).

	Control group	Treatment group	Control group < 100 kg
Previous antihypertensive treatment, yes/no	5/9	11/2	4/4
Males/females	7/7	3/10	3/5
Cholecystectomy/Hernia repair	11/3	11/2	7/1
Age (years)	59 $\pm$ 7	56 $\pm$ 9	62 $\pm$ 5
Weight (kg)	92 $\pm$ 18*	70 $\pm$ 9	79 $\pm$ 12
BSA (m ²)	2.0 $\pm$ 0.2**	1.8 $\pm$ 0.2	1.9 $\pm$ 0.1
<u>Premedication (mg)</u>			
Morphine	8.4 $\pm$ 1.9	8.5 $\pm$ 3.0	7.8 $\pm$ 1.6
Hyoscine	0.34 $\pm$ 0.07	0.34 $\pm$ 0.12	0.31 $\pm$ 0.06
<u>Anaesthetic drugs (mg kg⁻¹)</u>			
Thiopentone	2.3 $\pm$ 0.4	2.2 $\pm$ 0.2	2.4 $\pm$ 0.4
Fentanyl	0.008 $\pm$ 0.002	0.007 $\pm$ 0.002	0.007 $\pm$ 0.001
Pancuronium	0.1 $\pm$ 0.01	0.1 $\pm$ 0.005	0.1 $\pm$ 0.004
Neostigmine	0.03 $\pm$ 0.007	0.03 $\pm$ 0.004	0.03 $\pm$ 0.008
<u>Time intervals (min)</u>			
Premedication - anaesthesia	153 (85 - 240)	150 (75 - 190)	156 (120 - 230)
Induction - intubation	3.5 (2.0-5.0)	2.5 (2.0-4.0)	3.0 (2.0-4.0)
Induction - skin incision	32 (23 - 64)	35 (21 - 78)	30 (23 - 64)
Skin incision - closure	76 (51 - 276)	75 (34 - 128)	74 (43 - 147)
Skin closure - extubation	20 (5 - 32)	16 (10 - 30)	20 (11 - 32)

This complication was unexpected as there had been no signs of cardiac failure during anaesthesia and surgery. Furthermore, systolic arterial pressure had remained below 160 mm Hg, except for a short peak of 195 mm Hg during skin incision. The patient recovered quickly after receiving oxygen, frusemide, theophyllamine and phentolamine. Because of low respiratory rate, two patients in the metoprolol group received naloxone shortly after the postextubation measurement sequence. Otherwise, the postoperative course was uneventful and the patients were discharged from the recovery room after 4-5 hours (range 2-18). Discharge from the hospital usually occurred 2-3 days after surgery (range 1-9).

Arterial pressure (Fig 1 and 2). Just before starting metoprolol or placebo treatment MAP was 131 ± 10 mm Hg ($m \pm 1$ SD) (range 117-145 mm Hg) among the controls and 126 ± 10 (range 110-145) mm Hg in the metoprolol group (n.s.). The corresponding figures for systolic arterial pressure were 178 ± 20 (range 155-225) mm Hg and 171 ± 16 (range 140-195) mm Hg (n.s.) and for diastolic pressure 108 ± 7 (range 95-120) and 103 ± 9 (range 90-120) (n.s.).

Before anaesthesia, MAP in the two groups was not significantly different, but during intubation maximum pressure was 36 mm Hg greater among the controls ($p < 0.05$). MAP among the controls was significantly greater also during undisturbed anaesthesia ($p < 0.05$) and after extubation ($p < 0.01$). However, the difference was not quite significant ($p = 0.055$) after 20 min of surgery. The increase in MAP, in response to surgery, was about the same in both groups. The statistical conclusions were similar when analyzing systolic pressure. When comparing the metoprolol group with controls weighing less than 100 kg, the differences in arterial pressure

were significant also during surgery. A hypertensive episode as defined by Goldman & Caldera (1979) (SAP above 200 mm Hg, or an increase in SAP by more than 50 mm Hg above the preanaesthetic value) was seen in 10 patients of the control group and in 5 patients in the metoprolol group. Hypotensive episodes (SAP below 70 mm Hg) were seen in 1 patient among the controls and in 2 patients in the metoprolol group, in all cases during undisturbed anaesthesia.

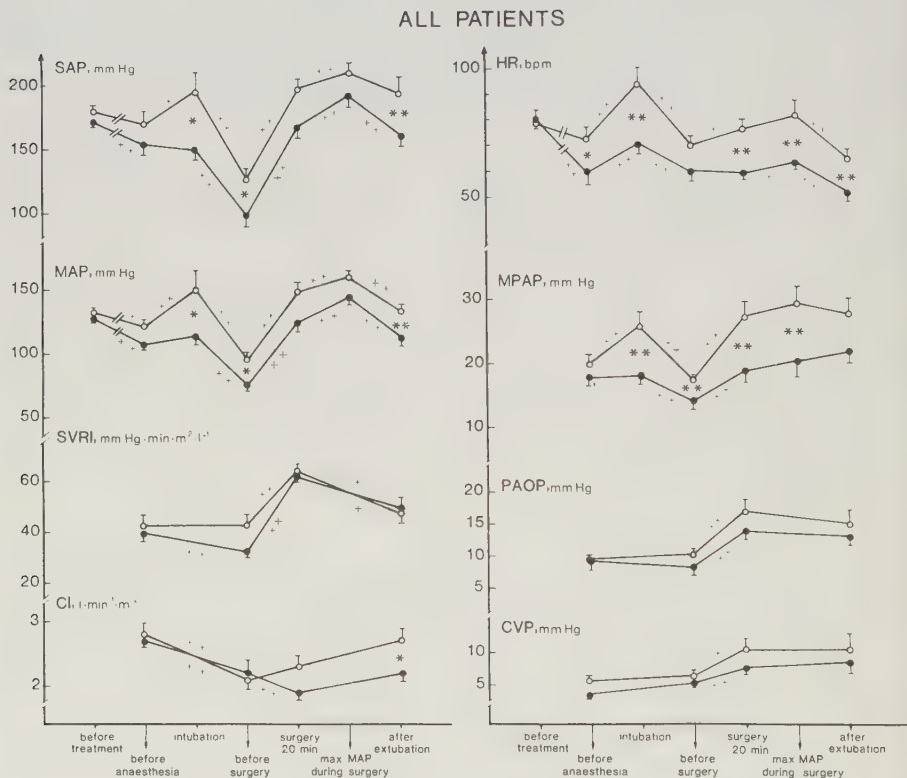


Fig. 1. Comparison of hemodynamic values among patients receiving metoprolol (●) or placebo (○). Group means $\pm$ 1 SEM. Significant differences between the groups are indicated: * = $p < 0.05$, ** = $p < 0.01$. Significant changes between successive stages, within each group, are indicated as + = $p < 0.05$, ++ = $p < 0.01$.

During surgery, two patients in the control group responded with very high blood pressure (MAP = 208 and 180 mm Hg), which did not decrease after administration of supplementary fentanyl (0.2 mg). One of the patients (MAP = 208 mm Hg) showed simultaneously high MPAP (46 mm Hg) with high pulmonary vascular resistance index (PVRI = 21 mm Hg min² l⁻¹) but PAOP was normal (8 mm Hg). Sodium nitroprusside (SNP) infusion, 0.5 µg kg⁻¹min⁻¹, was started. This resulted in a prompt decrease of MAP and MPAP. SNP was discontinued 20-30 min before the end of surgery. SNP

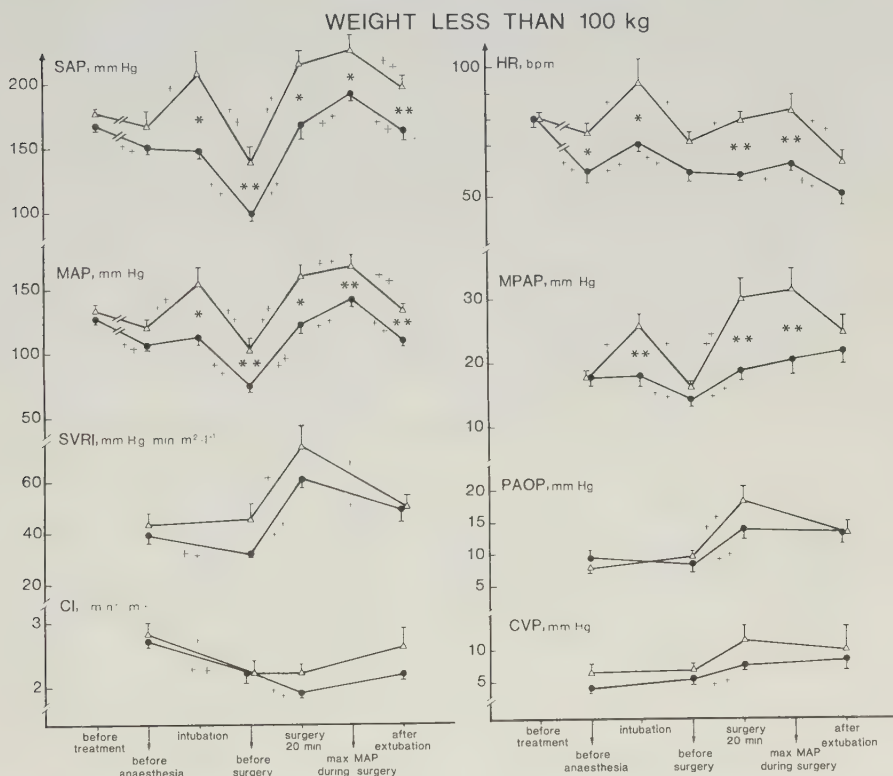


Fig. 2. Comparison of hemodynamic values among patients receiving placebo, weighing less than 100 kg (Δ) and metoprolol patients (●). Group means $\pm$ 1 SEM. Significant differences between the groups are indicated: * = $p < 0.05$, ** = $p < 0.01$, are indicated as + = $p < 0.05$, ++ = $p < 0.01$.

was not infused during the measurements. After one hour in the recovery room, systolic pressure was significantly less in the metoprolol group than among the controls ($p < 0.01$) (table III).

Table III. Systolic arterial pressure (mmHg) (mean $\pm$ 1 SD) in the recovery room. Significant changes between successive stages, within each group, are indicated as ++ = $p < 0.01$ and significant differences between the groups are indicated as * or ** ($p < 0.05$ or 0.01 , resp).

	On arrival		After 1 hour	After 2 hours	On discharge (after 4-5 h)
Control group	147 $\pm$ 23		140 $\pm$ 21 **	137 $\pm$ 27	134 $\pm$ 26
Treatment group	132 $\pm$ 28	++	114 $\pm$ 21 *	115 $\pm$ 14	115 $\pm$ 11
Control group < 100 kg	148 $\pm$ 21		142 $\pm$ 8	135 $\pm$ 31	125 $\pm$ 19

Heart rate (fig 1 and 2). This was significantly reduced by metoprolol. After the injection of neostigmine and atropine a heart rate below 40 min⁻¹ was observed in 4 patients of the metoprolol group but not in any of the controls. The minimum value was 26 min⁻¹. Additional atropine, 0.5 mg in repeated doses, was given without distinct improvement and the heart rate remained low in this patient during the first 2 hours in the recovery room (35-40 min⁻¹). The ECG showed sinus rhythm. Systolic arterial pressure was 85-90 mm Hg.

Cardiac index (CI) (fig 1 and 2). Before anaesthesia, CI in the two groups was similar and there were similar, statistically significant decreases ($p < 0.01$) in both groups during undisturbed anaesthesia. During surgery, CI decreased further, by $0.3 \text{ l min}^{-1} \text{ m}^{-2}$, among patients given metoprolol ($p < 0.01$). The change among the controls was not significant, nor the difference between the groups. After extubation, CI was significantly less in the metoprolol group. Except after extubation, statistical comparison between the metoprolol group and the controls weighing less than 100 kg yielded similar results as comparison with the whole group of controls.

Systemic vascular resistance index (SVRI) (fig 1 and 2). Before anaesthesia, this was about the same in both groups. In the metoprolol group, SVRI decreased significantly during undisturbed anaesthesia ($p < 0.01$), while it was approximately unchanged in the control group. The difference between the groups was not significant. During surgery, mean SVRI increased by 50 % among the controls, and by 91 % in the metoprolol group. The increase in both groups was significant ($p < 0.01$), with no significant difference between the groups.

Central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP) (fig 1 and 2). These measures increased significantly in response to surgery in both groups. Among patients receiving metoprolol, there was a significant correlation between the increase in PAOP and the increase in MAP in response to surgery ($r = 0.72$, $p < 0.01$). A similar correlation was found between increases in PAOP and increases in SVRI ($r = 0.69$, $p < 0.01$). In the control group no such correlation existed ($r = 0.17$ and $r = 0.05$, resp.). During surgery PAOP was 17 ± 6 mm Hg in the control group. Mean value during anaesthesia and surgery were 1-3 mm Hg less in

the metoprolol group, than among the controls, but the difference was not significant.

Pulmonary arterial pressure (fig 1 and 2). Before anaesthesia, mean pulmonary arterial pressure (MPAP) was 20 ± 6 mm Hg among the controls and 18 ± 5 mm Hg in the metoprolol group (n.s.). During intubation, the mean value for MPAP increased by 6 mm Hg ($p < 0.01$) among the controls, but was unchanged in the metoprolol group. The mean change in diastolic pulmonary arterial pressure (not shown) was + 7 ($p < 0.01$) and + 1 (n.s.) mm Hg, respectively. MPAP was significantly less in the metoprolol group at all stages during anaesthesia and surgery. The increase in MPAP in response to surgery was significant in both groups ($p < 0.01$).

Pulmonary vascular resistance index (PVRI) (mm Hg min m^2 l^{-1}). In the control group PVRI was 3.9 ± 1.6 (mean $\pm$ 1 SD) before anaesthesia, 3.7 ± 1.6 during undisturbed anaesthesia, 4.9 ± 5.0 during surgery and 4.9 ± 1.9 after extubation. The corresponding values in the metoprolol group were 3.2 ± 1.2 , 2.6 ± 1.1 , 2.6 ± 1.4 and 4.3 ± 2.2 , respectively. The only significant difference ($p < 0.05$) between the groups was seen during surgery. The values among controls weighing less than 100 kg were 3.7 ± 1.0 , 3.2 ± 1.2 , 6.0 ± 6.7 and 4.4 ± 1.3 , respectively.

ECG. One patient had chronic atrial fibrillation, the others were in sinus rhythm. Ventricular extrasystoles (VES) were observed during intubation or during surgery in 4 controls and in one patient receiving metoprolol. All of these patients, except one control patient, already had VES before anaesthesia. No new ST changes were observed.

Arterial PCO₂ (PaCO₂) and arterial and mixed venous PO₂ (PaO₂ and PvO₂) (table IV). Before anaesthesia, PaCO₂ was significantly ($p < 0.05$) greater in the metoprolol group than in the control group. During anaesthesia, the relation was reversed so that mean PaCO₂ was greater among the controls. This was in spite of a similar ventilatory minute volume, in relation to body surface area, in both groups. After extubation, mean PaCO₂ in the metoprolol group indicated that there was slight hypoventilation. PaCO₂ at this stage was 0.7 kPa greater than among the controls ($p < 0.05$). The difference in PaCO₂ between the metoprolol group and controls, who weighed less than 100 kg, was not significant. Before anaesthesia, mean PaO₂ and mean PvO₂ were similar in both groups. During undisturbed anaesthesia PaO₂ increased by 3.2-3.5 kPa ($p < 0.01$) in both groups, whereas mean PvO₂ was unchanged. As surgery commenced PaO₂ was unchanged in both groups while PvO₂ decreased significantly ($p < 0.05$) in the metoprolol group but not in the control group. After extubation, PaO₂ and PvO₂ was rather low in both groups during the measurements period, when the patients temporarily breathed room air without oxygen supplementation.

Plasma metoprolol concentration. The mean value was 662 nmol l⁻¹ (range 171-1180) before the 15 mg i.v. dose of metoprolol and 986 nmol l⁻¹ (range 396-1420) after this dose had been given; shortly before anaesthesia. The corresponding values after extubation were 792 nmol l⁻¹ (range 204-1440).

Table IV. Blood gas tensions, kPa (mean $\pm$ 1 SD). *, ** = significant difference between the control and treatment group (p < 0.05 and 0.01, resp.)

	Before anaesthesia	Before surgery	Surgery 20 min	After extubation
<u>Arterial PCO₂</u>				
Control group (n = 14)	5.2 $\pm$ 0.4	4.6 $\pm$ 0.3	4.5 $\pm$ 0.4	5.7 $\pm$ 0.8
	*		**	*
Treatment group (n = 13)	5.5 $\pm$ 0.6	4.3 $\pm$ 0.3	4.1 $\pm$ 0.4	6.4 $\pm$ 0.8
Control group < 100 kg (n = 8)	5.3 $\pm$ 0.4	4.4 $\pm$ 0.3	4.3 $\pm$ 0.4	5.4 $\pm$ 0.9
<u>Arterial PO₂</u>				
Control group (n = 14)	9.7 $\pm$ 1.1	13.2 $\pm$ 3.1	12.7 $\pm$ 3.2	8.2 $\pm$ 1.5
Treatment group (n = 13)	9.8 $\pm$ 1.6	13.0 $\pm$ 2.4	13.1 $\pm$ 2.4	7.0 $\pm$ 1.4
		*		
Control group < 100 kg (n = 8)	10.1 $\pm$ 0.9	15.2 $\pm$ 2.0	15.0 $\pm$ 2.1	8.3 $\pm$ 2.0
<u>Mixed venous PO₂</u>				
Control group (n = 14)	4.9 $\pm$ 0.5	4.8 $\pm$ 0.4	5.0 $\pm$ 0.4	4.4 $\pm$ 0.5
Treatment group (n = 13)	5.0 $\pm$ 0.3	4.9 $\pm$ 0.4	4.6 $\pm$ 0.5	4.0 $\pm$ 0.5
Control group < 100 kg (n = 8)	5.0 $\pm$ 0.5	4.9 $\pm$ 0.4	5.0 $\pm$ 0.2	4.2 $\pm$ 0.6

DISCUSSION

It is not uncommon that hypertension is discovered only shortly before the intended time for surgery. This poses a problem for the anaesthetist, who will have to decide whether to manage without treatment, whether to institute a short term of treatment with a drug and dosage believed suitable, or whether to postpone surgery so that antihypertensive treatment can be optimized, a procedure which may take several months. Although these matters have been widely discussed, there have been no randomized trials to determine the advantages and disadvantages of various policies. With the present study, we aimed at comparing the first and second of these alternatives. The treatment period (about 3 weeks) that we chose was the result of various compromises. In practice, we would suspect that there is often less time in which to treat the patient, if the operating schedule and the patient's plans are not to be disrupted. We chose a cardioselective betablocker, since this is the commonest type of antihypertensive drug in Sweden and several other countries. In addition, Prys-Roberts and others (1973) stated that pretreatment with a cardioselective betablocker (practolol) improved haemodynamic stability in anaesthetized hypertensive patients.

One factor which affects the interpretation of the present study is that more than half of the patients had had previous antihypertensive treatment, which had been withdrawn 2-3 weeks before starting metoprolol or placebo pretreatment. These patients were included in order to recruit sufficient numbers. Patients who had had previous antihypertensive treatment (which was stopped 2-3 weeks earlier), and those who were not previously treated had the same MAP (mean 129 and 128 mm Hg, respectively) before starting to take metoprolol or placebo tablets. An additional 2-5

weeks elapsed until the day of surgery. However, it may take longer for the effects of antihypertensive therapy to wear off completely (Vedin et al., 1973). Another problem is the skewness between the groups in respect of weight and arterial PCO₂ during anaesthesia. We circumvented this problem by presenting the results both with and without the six heaviest patients (>100 kg), all in the control group. By excluding these patients, the skewness was largely eliminated, while the findings in respect of haemodynamics were essentially unchanged.

The mean value and interindividual variation in plasma metoprolol concentration in this study agree with the findings of Johansson and colleagues (1980) on the effects of oral metoprolol, administered in slow release form. We gave an additional 15 mg of metoprolol i.v. shortly before anaesthesia. Both the subsequent measurements of plasma metoprolol concentration (von Bahr et al., 1976), and the heart rate suggest that the betablockade was adequate.

The findings during endotracheal intubation deserve special comment. In the present study, metoprolol pretreatment significantly reduced arterial pressure, which agrees with previous findings (Magnusson et al., 1983). In 1973 Prys-Roberts and his colleagues suggested that betablocker pretreatment might reduce the arterial pressure response to intubation, and this has since been corroborated by others as regards oral pretreatment (Pont  n et al., 1982). The suggestion that i.v. betablocker pretreatment reduces arterial pressures during intubation has not been confirmed, however. In fact, two studies using a relatively large dose of practolol (0.4 mg kg⁻¹) before thiopentone/suxamethonium induction found no significant effect of the betablocker on the arterial pressure response to intubation (Siedlecki, 1975; Werner et al., 1980). Thus, it appears that a

single i.v. dose of betablocker may be less effective than oral pretreatment, in attenuating the hypertensive response to intubation.

In the present study, metoprolol pretreatment significantly reduced arterial pressure both during undisturbed anaesthesia, during intubation and after extubation. There was a similar, but not quite significant difference during surgery (fig 1). However, the drug did not attenuate the increase in arterial pressure, in response to surgery, nor did metoprolol significantly attenuate the variations in SVRI. In this respect, our findings are similar to those of Pontén and colleagues (1982), who compared patients in whom betablockers were withdrawn 48 hours before surgery, with patients in whom betablockers were continued. The findings differ from the study by Prys-Roberts and others (1971), who studied treated and untreated hypertensive patients in a non-randomized study. Comparison with their study is difficult, however, because they did not measure haemodynamics during surgery and because antihypertensive treatment in their study included other drugs, such as bethanidine, methyl dopa and reserpine. Since the heart is the major site of action for metoprolol, our finding that variations in SVRI were not attenuated is not very surprising. It is notable that CI decreased significantly in the metoprolol group, as surgery commenced, while it was unchanged among the controls. Furthermore, the increase in PAOP in the metoprolol group was significantly correlated to the increases in SVRI and MAP. This might indicate that the betablocked heart could not respond adequately to the of increased afterload, but on the other hand the mean increase in PAOP at e this stage was as great among the controls. The anaesthetic technique used for the present study reflects the usual practice at our clinic at the time. The results show that this was inadequate and we now usually add halothane, or enflurane, to avoid perioperative hypertension. The high

PaCO₂ after extubation, particularly in the metoprolol group suggests that addition of more fentanyl peroperatively would not have been a suitable way of deepening anaesthesia.

After extubation, metoprolol reduced arterial pressure and also cardiac index. Myocardial oxygen demand was thus reduced, which we regard as an advantage at this stage when the anaesthetist's control of the ventilation and oxygen supply is less certain than with the endotracheal tube in place. In fact, PaO₂ was rather low at the postextubation measurement, when the patient temporarily breathed room air without oxygen supplementation. One drawback with metoprolol was the marked bradycardia after neostigmine in some patients.

We conclude that metoprolol pretreatment reduced arterial pressure and heart rate in hypertensive patients operated on under fentanyl/nitrous oxide anaesthesia, and that metoprolol was well tolerated except for occasional bradycardia after neostigmine. The marked variations in arterial pressure, SVRI and PAOP in both groups suggest that drugs or anaesthetic techniques which attenuate variations in systemic vascular resistance would have been beneficial.

ACKNOWLEDGEMENT

This study was supported by grants from the Medical Faculty, University of Lund, Sweden. Thanks are due to Hässle/Astra AB, Gothenburg, for valuable support and the metoprolol assays, to Mrs Ingrid Svenstam for excellent technical assistance and to Dr Roger Fletcher for analysing the ECG records.

REFERENCES

- DuBois, D., and DuBois, E.F. (1916). A formula to estimate the approximate surface area if height and weight be known. Arch. Int. Med., 17, 863.
- Ervik, M. (1975). Quantitative determination of metoprolol in plasma and urine by gas chromatography. Acta pharmacol. Toxicol. (Cph), 36, (suppl. V), 136.
- Goldman, L., and Caldera, D.L. (1979). Risks of general anesthesia and elective operation in the hypertensive patient. Anesthesiology, 50, 285.
- Johnsson, G., Jordö, L., Lundborg, P., Regårdh, C-G., and Rönn, O. (1980). Plasma levels and pharmacological effects of metoprolol administered as controlled release (Durules) and ordinary tablets in healthy volunteers. Int. J. Clin. Pharmacol., Ther. Toxicol., 18, 292.
- Magnusson, J., Werner, O., Carlsson, C., Nordén, N., and Pettersson, K-I. (1983). Metoprolol, fentanyl and stress response to microlaryngoscopy. Effects on arterial pressure, heart rate and plasma concentrations of catecholamines, ACTH and cortisol. Br. J. Anaesth., 55, 405.
- Pontén, J., Biber, B., Henriksson, B-Å., Hjalmarsson, Å., Jonsteg, C., and Lundberg, D. (1982). Betareceptor blockade and neurolept anaesthesia. Withdrawal vs continuation of long-term therapy in gall-bladder and carotid artery surgery. Acta anaesth. scand., 26, 576.
- Prys-Roberts, C., Meloche, R., and Foëx, P. (1971). Studies of anesthesia in relation to hypertension I: Cardiovascular responses of treated and untreated patients. Br. J. Anaesth., 43, 122.
- Prys-Roberts, C., Foëx, P., Biro, G.P., and Roberts, J.G. (1973). Studies of anaesthesia in relation to hypertension. V: Adrenergic beta-receptor blockade. Br. J. Anaesth., 45, 671.

- Siedlecki, J. (1975). Disturbances in the function of cardiovascular system in patients following endotracheal intubation and attempts of their prevention by pharmacological blockade of sympathetic system. Anesth. Resusc. Intens. Ther., 3, 107.
- Vedin, J.A., Wilhelmsson, C.-E., and Werkö, L. (1973). Comparative study of alprenolol and methyl dopa in previously untreated essential hypertension. Br. Heart. J., 35, 1285.
- von Bahr, C., Collste, P., Frisk-Holmberg, M., Haglund, K., Jorfelt, L., Orme, M., Östman, J., and Sjöqvist, F. (1976). Plasma levels and effects of metoprolol on blood pressure, adrenergic beta receptor blockade, and plasma renin activity in essential hypertension. Clin. Pharm. and Therap., 20, 130.
- Werner, O., Magnusson, J., Fletcher, R., Nilsson-Ehle, P., and Pahlm, O. (1980). I.v. practolol during microlaryngoscopy. Effect on arterial pressure, heart rate, blood glucose and lipolysis. Br. J. Anaesth., 52, 91.
- Werner, O., and Benthin, M. (1982). Mean intravascular pressure without tears. Simultaneous recording of the unfiltered pressure curve, and of mean pressure. Anaesthesia, 37, 836.

